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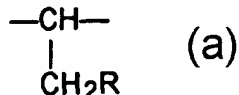
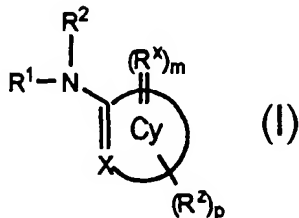
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(54) Title: ENAMINE DERIVATIVES

(57) Abstract: Enamine derivatives of formula (1) are described. In said for-
mula, R¹ a group Ar¹L²Ar²Alk- in which Ar¹ is an aromatic or heteroaromatic
group, L² is a covalent bond or a linker atom or group, Ar² is an arylene or het-
eroarylene group and Alk is a chain -CH₂-CH(R)-, -CH=C(R)- or (a) in which
R is a carboxylic acid or a derivative or biostere thereof; R² is a hydrogen atom
or a C₁₋₆alkyl group; Cy is a cycloaliphatic or heterocycloaliphatic ring in which
X is a N atom or a C(R^w) group; R^x is a oxo, thioxo, or imino group; R^w and
R^z are each a hydrogen atom or optional substituent; provided that Cy is not a
cyclobutenedione group; and the salts, solvates, hydrates and N-oxides thereof.
The compounds are able to inhibit the binding of integrins to their ligands and are
of use in the prophylaxis and treatment of immune or inflammatory disorders, or
disorders involving the inappropriate growth or migration of cells.

ENAMINE DERIVATIVES

This invention relates to a series of enamine derivatives, to compositions
5 containing them, to processes for their preparation, and to their use in
medicine.

Over the last few years it has become increasingly clear that the physical
interaction of inflammatory leukocytes with each other and other cells of
10 the body plays an important role in regulating immune and inflammatory
responses [Springer, T. A., *Nature*, 346, 425, (1990); Springer, T. A., *Cell*,
76, 301, (1994)]. Specific cell surface molecules collectively referred to as
cell adhesion molecules mediate many of these interactions.

15 The adhesion molecules have been sub-divided into different groups on
the basis of their structure. One family of adhesion molecules which is
believed to play a particularly important role in regulating immune and
inflammatory responses is the integrin family. This family of cell surface
glycoproteins has a typical non-covalently linked heterodimer structure. At
20 least 16 different integrin alpha chains and 8 different integrin beta chains
have been identified [Newman, P. *et al*, *Molecular Medicine Today*, 304,
(1996)]. The members of the family are typically named according to their
heterodimer composition although trivial nomenclature is widespread in the
field. Thus the integrin $\alpha 4\beta 1$ consists of the integrin alpha 4 chain
25 associated with the integrin beta 1 chain, but is also widely referred to as
Very Late Antigen 4 or VLA-4. Not all of the potential pairings of integrin
alpha and beta chains have yet been observed in nature and the integrin
family has been subdivided into a number of subgroups based on the
pairings that have been recognised to date [Sonnenberg, A., *Current*
30 *Topics in Microbiology and Immunology*, 184, 7, (1993)].

The importance of integrin function in normal physiological responses is
highlighted by two human deficiency diseases in which integrin function is
defective. Thus in the disease termed Leukocyte Adhesion Deficiency
35 (LAD) there is a defect in one of the families of integrins expressed on
leukocytes [Marlin, S. D. *et al*, *J. Exp. Med.* 164, 855, (1986)]. Patients

suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections, which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting (Hodivala-Dilke, K. M., J. Clin. Invest. 103, 229, (1999)).

The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B., J. Immunol. 149, 3394, (1992); Li, Z. *et al*, Am. J. Physiol. 263, L723, (1992); Mitjans, F. *et al*, J. Cell Sci. 108, 2825, (1995); Brooks, P. C. *et al*, J. Clin. Invest. 96, 1815, (1995); Binns, R. M. *et al*, J. Immunol. 157, 4094, (1996); Hammes, H.-P. *et al*, Nature Medicine 2, 529, (1996); Srivata, S. *et al*, Cardiovascular Res. 36, 408 (1997)]. A number of monoclonal antibodies which block integrin function are currently being investigated for their therapeutic potential in human disease, and one, ReoPro, a chimeric antibody against the platelet integrin α IIb β 3 is in use as a potent anti-thrombotic agent for use in patients with cardiovascular complications following coronary angioplasty.

Integrins recognize both cell surface and extracellular matrix ligands, and ligand specificity is determined by the particular alpha-beta subunit combination of the molecule [Newman, P., *ibid*]. One particular integrin subgroup of interest involves the α 4 chain which can pair with two different beta chains β 1 and β 7 [Sonnenberg, A., *ibid*]. The α 4 β 1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes, eosinophils and basophils) although it is absent or only present at low levels on circulating neutrophils. α 4 β 1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L., Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*, Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α 4 β 1 and ligands on other cells and the extracellular matrix plays

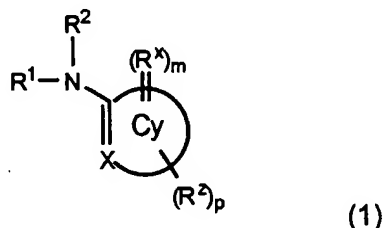
an important role in leukocyte migration and activation [Yednock, T. A. *et al*, *Nature*, 356, 63, (1992); Podolsky, D. K. *et al*, *J. Clin. Invest.* 92, 372, (1993); Abraham, W. M. *et al*, *J. Clin. Invest.* 93, 776, (1994)].

- 5 The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B. and Weissman, I. L., *EMBO J.* 8, 1735, (1989)]. The $\alpha 4\beta 7$ pairing is expressed on certain sub-populations of T and B lymphocytes and on eosinophils [Erle, D. J. *et al*, *J. Immunol.* 153, 517 (1994)]. Like $\alpha 4\beta 1$, $\alpha 4\beta 7$ binds to VCAM-1 and fibronectin. In addition,
- 10 $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, *Cell*, 74, 185, (1993)]. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important sites of inflammation outside of mucosal tissue [Yang, X.-D. *et al*, *PNAS*, 91, 12604, (1994)].
- 15 Regions of the peptide sequence recognized by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises
- 20 a LDT sequence in MAdCAM-1 [Birskin, M. J. *et al*, *J. Immunol.* 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al*, *J. Biol. Chem.*, 269, 18668, (1994); Shorff, H. N. *et al*, *Biorganic Med. Chem. Lett.*, 6, 2495, (1996); Vanderslice, P. *et al*, *J.*
- 25 *Immunol.*, 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A., *et al*, *PNAS*, 88, 8072, (1991)].
- 30 Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is important to be able to identify selective
- 35 inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of α_4 integrins. Members of the group are able to inhibit α_4 integrins such as $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. These compounds possess the additional advantage of good pharmacokinetic properties, especially low plasma clearance.

Thus according to one aspect of the invention we provide a compound of formula (1)

10



wherein

R¹ is a group Ar¹L²Ar²Alk- in which Ar¹ is an optionally substituted aromatic or heteroaromatic group, L² is a covalent bond or a linker atom or group, Ar² is an optionally substituted arylene or heteroarylene group and Alk is a chain -CH₂-CH(R)-, -CH=C(R)-, —CH—

|
CH₂R

in which R is a carboxylic acid (-CO₂H) or a derivative or biostere thereof;

R² is a hydrogen atom or a C₁₋₆alkyl group;

the ring Cy is an unsaturated cycloaliphatic or heterocycloaliphatic ring containing X, in which X is a N atom or a C(R^w) group;

R^w is a group R^z;

R^x which may be present on any available carbon atom of the ring Cy is a oxo (=O), thioxo (=S) or imino (=NR³⁰) group in which R³⁰ is an aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or hetero-aromatic group;

m is zero or the integer 1, 2 or 3;

R^z which may be present on any available carbon or nitrogen atom of the ring Cy is selected from a halogen atom or -(Alk⁴)_vL¹(Alk¹)_nR³ in which Alk⁴ is a straight or branched C₁₋₃alkylene chain, v is zero or the integer 1,

L¹ is a covalent bond or a link r atom or group, n is zero or the integer 1, Alk¹ is an optionally substituted aliphatic chain and R³ is a hydrogen atom or a -CN, -NO₂ or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group;
5 p is zero or the integer 1, 2, 3 or 4;
provided that Cy is not a cyclobutenedione group;
and the salts, solvates, hydrates and N-oxides thereof.

10 It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures
15 thereof, unless stated or shown otherwise.

Optionally substituted aromatic groups represented by Ar¹ when present in the group R¹ include for example optionally substituted monocyclic or bicyclic fused ring C₆₋₁₂ aromatic groups, such as phenyl, 1- or 2-naphthyl,
20 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optionally substituted heteroaromatic groups represented by the group Ar¹ when present in the group R¹ include for example optionally substituted C₁₋₉ heteroaromatic groups containing for example one, two, three or four
25 heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen,
30 sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

35 Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl,

isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalyl, naphthyridinyl, e.g. 2,6-naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Each aromatic or heteroaromatic group represented by the group Ar^1 may be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which L^3 and L^4 , which may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{6-12} aromatic or C_{1-9} heteroaromatic, $-OR^5$ [where R^5 is a hydrogen atom, an optionally substituted C_{1-6} alkyl or C_{3-8} cycloalkyl group], $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, $-CN$, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom, an optionally substituted C_{1-6} alkyl or C_{3-8} cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^3 and L^4 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom

Optionally substituted C_{6-12} aromatic and C_{1-9} heteroaromatic groups represented by R^4 include those aromatic and heteroaromatic groups as described hereinbefore for the group Ar^1 . Optional substituents which may

be present on these groups include those R¹³ optional substituents as described hereinafter.

- When L³ and/or L⁴ is present in these substituents as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R⁸)- [where R⁸ is a hydrogen atom or an optionally substituted straight or branched C₁₋₆alkyl group], -CON(R⁸)-, -OC(O)N(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, -N(R⁸)O-, -ON(R⁸)-, -N(R⁸)N(R⁸)-, -N(R⁸)CON(R⁸)-, -N(R⁸)CSN(R⁸)-, or -N(R⁸)SO₂N(R⁸)- groups. Where the linker group contains two R⁸ substituents, these may be the same or different.
- 15 When R⁴, R⁵, R⁶, R⁷ and/or R⁸ is present as a C₁₋₆alkyl group it may be a straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a methyl or ethyl group. C₃₋₆cycloalkyl groups represented by R⁴, R⁵, R⁶, R⁷ and/or R⁸ include C₃₋₆cycloalkyl groups e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁₋₆alkoxy e.g. methoxy or ethoxy groups.
- 25 When the groups R⁵ and R⁶ or R⁶ and R⁷ are both C₁₋₆alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or -N(R⁵)-. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When Alk² is present as an aliphatic or heteroaliphatic chain it may be for example any divalent chain corresponding to the below-mentioned aliphatic or heteroaliphatic group described for Alk¹ or R³ respectively.

Halogen atoms represented by R^4 in the optional Ar^1 substituents include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by $-L^3(Alk^1)_tL^4(R^4)_u$ when present in Ar^1 groups in compounds of the invention include atoms or groups $-L^3Alk^2L^4R^4$, $-L^3Alk^2R^4$, $-L^3R^4$, $-R^4$ and $-Alk^2R^4$ wherein L^3 , Alk^2 , L^4 and R^4 are as defined above. Particular examples of such substituents include $-L^3CH_2L^4R^4$, $-L^3CH(CH_3)L^4R^4$, $-L^3CH(CH_2)_2L^4R^4$, $-L^3CH_2R^4$, $-L^3CH(CH_3)R^4$, $-L^3(CH_2)_2R^4$, $-CH_2R^4$, $-CH(CH_3)R^4$, $-(CH_2)_2R^4$ and $-R^4$ groups.

Thus Ar^1 in compounds of the invention may be optionally substituted for example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{3-8} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, carboxy C_{1-6} alkyl, e.g. carboxyethyl, C_{1-6} alkylthio e.g. methylthio or ethylthio, carboxy C_{1-6} alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxy-propylthio, C_{1-6} alkoxy, e.g. methoxy or ethoxy, hydroxy C_{1-6} alkoxy, e.g. 2-hydroxyethoxy, halo C_{1-6} alkyl, e.g. $-CF_3$, $-CHF_2$, CH_2F , halo C_{1-6} alkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, C_{1-6} alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), amino C_{1-6} alkyl, e.g. aminomethyl or aminoethyl, C_{1-6} dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6} alkylamino C_{1-6} alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylamino C_{1-6} alkyl, e.g. diethylaminoethyl, amino C_{1-6} alkoxy, e.g. aminoethoxy, C_{1-6} alkylamino C_{1-6} alkoxy, e.g. methylaminoethoxy, C_{1-6} dialkylamino C_{1-6} alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylamino-propoxy, nitro, cyano, amidino, hydroxyl ($-OH$), formyl [$HC(O)-$], carboxyl ($-CO_2H$), $-CO_2Alk^3$ [where Alk^3 is as defined below for Alk^7], C_{1-6} alkanoyl e.g. acetyl, thiol ($-SH$), thio C_{1-6} alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), $-SO_3Alk^3$, C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6} dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6} alkyl-

aminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g. ethylaminothiocarbonylmethylamino, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

L² when present as part of the group R¹ in compounds of the invention may be a linker atom or group L^{2a} or a linker -(Alk^a)L^{2a}-, where Alk^a is an optionally substituted aliphatic or heteroaliphatic chain as previously defined for Alk², and L^{2a} is a linker atom or group as described above for L³ and L⁴.

Optionally substituted arylene groups represented by Ar² when present as part of the group R¹ include those aromatic groups as previously described for Ar¹.

Optionally substituted heteroarylene groups represented by Ar^2 when present as part of the group R^1 include those heteroaromatic groups as previously described for Ar^1 .

- 5 Each arylene or heteroarylene group represented by Ar^2 may be attached to the remainder of the molecule through any available ring carbon or nitrogen atoms.

10 The arylene and heteroarylene groups represented by Ar^2 may be optionally substituted by one, two or more substituents selected from the atoms or groups $-L^3(Alk^2)_tL^4(R^4)_u$ described herein. Where two of these atoms or groups are present they may be the same or different.

15 When the group R is present in R^1 in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include $-CO_2Alk^7$ and $-CONR^5R^6$ groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an
20 acylsulphonamide group.

Esters ($-CO_2Alk^7$) and amide ($-CONR^5R^6$) derivatives of the carboxylic acid group ($-CO_2H$) in compounds of formula (1) may advantageously be used as prodrugs of the active compound. Such prodrugs are compounds
25 which undergo biotransformation to the corresponding carboxylic acid prior to exhibiting their pharmacological effects and the invention particularly extends to produgs of the acids of formula (1). Such prodrugs are well known in the art, see for example International Patent Application No. WO00/23419, Bodor, N. (Alfred Benzon Symposium, 1982, 17, 156-177),
30 Singh, G. et al (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard, H., (Design of Prodrugs, 1985, Elsevier, Amsterdam).

Esterified carboxyl groups represented by the group $-CO_2Alk^7$ wherein Alk^7 include groups is a straight or branched optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group, an optionally substituted C_{2-8} alkenyl group such as a

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propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C₂₋₈alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C₃₋₈cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C₃₋₈cycloalkylC₁₋₈alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C₃₋₈heterocycloalkylC₁₋₆alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C₁₋₆alkyloxyC₁₋₆alkyl group such as a methoxyethyl or propoxyethyl group; an optionally substituted C₁₋₆alkylthioC₁₋₆alkyl group such as an ethylthioethyl group; an optionally substituted C₁₋₆alkylsulfinylC₁₋₆alkyl group such as a methylsulfinylethyl group; an optionally substituted C₁₋₆alkylsulfonylC₁₋₆alkyl group such as a methylsulfonylmethyl group; an optionally substituted C₃₋₈cycloalkyloxyC₁₋₆alkyl group such as a cyclohexyloxy-methyl group; an optionally substituted C₃₋₈cycloalkylthioC₁₋₆alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C₃₋₈cycloalkylsulfinylC₁₋₆alkyl group such as a cyclopentylsulfinylmethyl group; an optionally substituted C₃₋₈cycloalkylsulfonylC₁₋₆alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C₁₋₆alkyloxycarbonylC₁₋₆alkyl group such as isobutoxycarbonylpropyl group; an optionally substituted C₁₋₆alkyloxycarbonylC₁₋₆alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C₁₋₆alkyloxycarbonyloxyC₁₋₆alkyl group such as an isopropoxycarbonyloxyethyl e.g. a 1-(isopropoxycarbonyloxy)ethyl, 2-(isopropoxycarbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C₁₋₆alkyloxycarbonyloxyC₁₋₆alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C₃₋₈cycloalkyloxycarbonyloxyC₁₋₆alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C₁₋₈alkylaminoC₁₋₈alkyl group such as a N-dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C₆₋₁₂aryl-N-C₁₋₆alkylaminoC₁₋₆alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C₁₋₈alkylcarbamoylC₁₋₈alkyl group such as a N-diethylcarbamoylmethyl

group; an optionally substituted C₆₋₁₀arylC₁₋₆alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆₋₁₀aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₀aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C₆₋₁₂arylthioC₁₋₈alkyl group such as an optionally substituted phenylthioethyl group; a C₆₋₁₂arylsulfinylC₁₋₈alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C₆₋₁₂arylsulfonylC₁₋₈alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a acetoxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C₄₋₈imidoC₁₋₈alkyl group such as a succinimidomethyl or phthalamidoethyl group; a C₆₋₁₂aroxyloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C₁₋₈alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional substituents present on the Alk⁷ group include R^{13a} substituents described above.

Optional substituents which may be present on the Alk⁷ group include R^{13a} substituents as defined hereinafter.

When the group R² is present in compounds of the invention as a C₁₋₆alkyl group it may be for example a straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a methyl or ethyl group.

Unsaturated cycloaliphatic groups represented by the ring Cy include unsaturated C₄₋₁₀ cycloaliphatic groups. Particular examples of unsaturated cycloaliphatic groups represented by Cy include C₃₋₇cycloalkenyl groups.

Particular examples of unsaturated cycloaliphatic groups represented by Cy include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl groups.

Unsaturated heterocycloaliphatic groups represented by the ring Cy include unsaturated C₃₋₁₀ heterocycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀ heterocycloalkenyl e.g. C₃₋₇ heterocycloalkenyl groups, each of said groups containing one, two, three
5 or four heteroatoms or heteroatom containing groups L⁷ where L⁷ is as defined above for L³ where L³ is a linker atom or group. It will be appreciated that when X in the ring Cy is a nitrogen atom then a further heteroatom or heteroatom containing group L⁷ need not be present in the ring Cy.

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Particular examples of unsaturated heterocycloaliphatic groups represented by Cy include dihydrofuranyl, dihydrothiophenyl, 2,3-dihydrothiophene-1,1-dioxide, 3-amino-4,5-dihydro-1,1-dioxothiophenyl [where amino refers to the group NR¹R²], 3,4-dihydro-1,1-dioxo-2H-thiopyranyl,
15 2,3,4,5-tetrahydro-1,1-dioxo-thiopinyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, oxazolinyl, thia-zolinyl, imidazolinyl, pyrazolinyl, isoxazolinyl, isothiazolinyl, pyranyl, dihydropyridyl, tetrahydropyridyl, dihydropyridazinyl, tetrahydropyridazinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, dihydropyrazinyl, tetrahydro-pyrazinyl, dihydrotriazinyl, tetrahydrotriazinyl, oxazinyl or
20 dihydrothiadiazinyl group.

When the unsaturated cycloaliphatic or heterocycloaliphatic ring represented by Cy is substituted by a group R^x, R^x may be a oxo (=O), thioxo (=S) or imino (=NR³⁰) group. It will be understood that when the
25 ring Cy includes such a group R^x, then the corresponding hydroxy (-OH), thiol (-SH) or amino (-NHR³⁰) tautomers in which the double bond migrates to become part of the ring Cy are also included.

When the group R³⁰ is present in compounds of formula (1) as an aliphatic group it may be any aliphatic chain as described hereinafter for Alk¹ but with each containing a terminal hydrogen atom. When the group R³⁰ is present in compounds of formula (1) as a heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group it may be any heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or
30 heteroaromatic group as described hereinafter for the group R³. Optional substituents which may be present on these groups include any optional

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substituents described herein in relation to the corresponding Alk¹ aliphatic chains or R³ heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic groups.

- 5 The group R² when present may be attached to any suitable carbon or nitrogen atom of the unsaturated cycloaliphatic or heterocycloaliphatic ring represented by Cy.

10 Halogen atoms represented by the group R² include fluorine, chlorine, bromine and iodine atoms.

C₁₋₃ alkylene chains represented by Alk⁴ in the group R² in compounds of formula (1) include for example a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂- or -CH₂CH(CH₃)- chain.

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When present the linker atom or group represented by L¹ in the group R² in compounds of formula (1) may be any linker atom or group as described above for the linker atom or group L³.

- 20 When Alk¹ is present in the group R² in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C₁₋₁₀ aliphatic chain. Particular examples include optionally substituted straight or branched chain C₁₋₆ alkylene, C₂₋₆ alkenylene, or C₂₋₆ alkynylene chains.

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Particular examples of aliphatic chains represented by Alk¹ include optionally substituted -CH₂-, -(CH₂)₂-, -CH(CH₃)CH₂-, -(CH₂)₂CH₂-, -(CH₂)₃CH₂-, -CH(CH₃)(CH₂)₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂CH₂-, -(CH₂)₂C(CH₃)₂CH₂-, -(CH₂)₄CH₂-, -(CH₂)₅CH₂-,
 30 -CHCH-, -CHCHCH₂-, -CH₂CHCH-, -CHCHCH₂CH₂-, -CH₂CHCHCH₂-, -(CH₂)₂CHCH-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂- or -(CH₂)₂CCH- groups.

- 35 Heteroaliphatic groups represented by the group R³ when present in the group R² in compounds of formula (1) include the aliphatic chains just described for Alk¹ but with each containing a terminal hydrogen atom and

additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^5 where L^5 is as defined above for L^3 when L^3 is a linker atom or group. Each L^5 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-L^5CH_3$, $-CH_2L^5CH_3$, $-L^5CH_2CH_3$, $-CH_2L^5CH_2CH_3$, $-(CH_2)_2L^5CH_3$, $-(CH_2)_3L^5CH_3$, $-L^5(CH_2)_3$, and $-(CH_2)_2L^5CH_2CH_3$ groups.

- 10 The optional substituents which may be present on aliphatic chains or heteroaliphatic groups represented by Alk^1 and R^3 respectively or aliphatic groups represented by $-Alk^1R^3$ include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or $-OH$, $-CO_2H$, $-CO_2R^9$, where R^9 is an optionally substituted straight or branched C_{1-6} alkyl group as defined above for R^4 , $-CONHR^9$, $-CON(R^9)_2$, $-COR^9$, $-COCH_3$, C_{1-6} alkoxy, e.g. methoxy or ethoxy, halo C_{1-6} alkoxy e.g. $-OCF_3$, thiol, $-S(O)R^9$, $-S(O)_2R^9$, C_{1-6} alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^9$ and $-N(R^9)_2$ groups. Where two R^9 groups are present in any of the above substituents these may be the same or different.

- 25 Optionally substituted cycloaliphatic groups represented by the group R^3 when present in the group R^2 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g. C_{3-7} cycloalkenyl groups.

- 30 Optionally substituted heterocycloaliphatic groups represented by the group R^3 when present in the group R^2 include optionally substituted C_{3-10} heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10} heterocycloalkyl, e.g. C_{3-7} heterocycloalkyl, or C_{3-10} heterocycloalkenyl, e.g. C_{3-7} heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^5 as defined above.

Optionally substituted polycycloaliphatic groups represented by the group R^3 when present in the group R^2 include optionally substituted C₇₋₁₀ bi- or tricycloalkyl or C₇₋₁₀bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R^3 include the
 5 optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L⁵ atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group R^3
 10 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-
 15 dioxolanyl, imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl, pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, pyranal, e.g. 2- or 4-pyranal, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o-
 20 or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups
 25 represented by the group R^3 include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl or propyl, haloC₁₋₆alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF₃)₂, C₁₋₆alkoxy, e.g. methoxy, ethoxy or propoxy, haloC₁₋₆alkoxy, e.g. halomethoxy or haloethoxy such as
 30 difluoromethoxy or trifluoromethoxy, thiol, C₁₋₆alkylthio e.g. methylthio, ethylthio or propylthio, or -(Alk^{4a})_gR¹⁰ groups in which Alk^{4a} is a straight or branched C₁₋₃alkylene chain, g is zero or an integer 1 and R¹⁰ is a -OH, -SH, -N(R¹¹)₂, (in which R¹¹ is an atom or group as defined herein for R⁸) -CN, -CO₂R¹¹, -NO₂, -CON(R¹¹)₂, -CSN(R¹¹)₂, -COR¹¹,
 35 -CSN(R¹¹)₂, -N(R¹¹)COR¹¹, -N(R¹¹)CSR¹¹, -SO₂N(R¹¹)₂, -N(R¹¹)SO₂R¹¹,

-N(R¹¹)CON(R¹¹)₂, -N(R¹¹)CSN(R¹¹), N(R¹¹)SO₂N(R¹¹)₂ or optionally substituted phenyl group. Where two R¹¹ atoms or groups are present in these substituents these may be the same or different. Optionally substituted phenyl groups include phenyl substituted by one, two or three of the R¹³ groups described below

Additionally, when the group R³ is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group -(L⁶)_p(Alk⁵)_qR¹² in which L⁶ is -C(O)-, -C(O)O-, -C(S)-, -S(O)₂-, -CON(R¹¹)-, -CSN(R¹¹)- or SO₂N(R¹¹)-; p is zero or an integer 1; Alk⁵ is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R¹² is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycyclo-aliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

C₁₋₃alkylene chains represented by Alk^{4a} include those groups as previously described for Alk⁴.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk⁵ include those optionally substituted chains described above for Alk¹ and R³ respectively. Optional substituents which may be present on these groups include those described above in relation to Alk¹ and R³ aliphatic and heteroaliphatic chains.

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocycloaliphatic groups represented by R¹² include those groups just described for the group R³. Optional substituents which may be present on those groups include those described above in relation to R³ cycloaliphatic groups.

Aromatic or heteroaromatic groups represented by R¹² include those groups described herein for the group Ar¹. Optional substituents which may be present on these groups include those R¹³ optional substituents described hereinafter.

When the group R^3 is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group Ar^1 .

- 5 Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R^3 include one, two, three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-R^{13a}$ or $-Alk^6(R^{13a})_m$, where R^{13a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl ($-OH$),
- 10 substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{14}$ [where R^{14} is an $-Alk^6(R^{13a})_m$, aryl or heteroaryl group], $-CSR^{14}$, $-SO_3H$, $-SOR^{14}$, $-SO_2R^{14}$, $-SO_3R^{14}$, $-SO_2NH_2$, $-SO_2NHR^{14}$, $-SO_2N(R^{14})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{14}$, $-CSNHR^{14}$, $-CON[R^{14}]_2$, $-CSN(R^{14})_2$, $-N(R^{11})SO_2R^{14}$, $-N(SO_2R^{14})_2$,
- 15 $-NH(R^{11})SO_2NH_2$, $-N(R^{11})SO_2NHR^{14}$, $-N(R^{11})SO_2N(R^{14})_2$, $-N(R^{11})COR^{14}$, $-N(R^{11})CONH_2$, $-N(R^{11})CONHR^{14}$, $-N(R^{11})CON(R^{14})_2$, $-N(R^{11})CSNH_2$, $-N(R^{11})CSNHR^{14}$, $-N(R^{11})CSN(R^{14})_2$, $-N(R^{11})CSR^{14}$, $-N(R^{11})C(O)OR^{14}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C₅-7cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^{11})$ -, $-C(O)$ -, $-C(S)$ -, $S(O)$ or $-S(O)_2$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{11})SO_2NHet^1$, $-N(R^{11})CONHet^1$, $-N(R^{11})CSNHet^1$, $-SO_2N(R^{11})Het^2$ [where Het^2 is an optionally substituted monocyclic C₅-7carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{11})$ -, $-C(O)$ - or $-C(S)$ - groups], $-Het^2$, $-CON(R^{11})Het^2$, $-CSN(R^{11})Het^2$,
- 20 $-N(R^{11})CON(R^{11})Het^2$, $-N(R^{11})CSN(R^{11})Het^2$, cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk^6 is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{15})$ - groups [where R^{15} is a hydrogen atom or C₁₋₆alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{11} or R^{14} groups are present in one of the above substituents, the R^{11} or R^{14} groups may be the same or different.
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- 30
- 35 When in the group $-Alk^6(R^{13a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on

any suitable carbon atom in -Alk^6 . Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^6 . Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^6 becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group -NHR^{14} [where R^{14} is as defined above] or a group $\text{-N(R}^{14})_2$ wherein each R^{14} group is the same or different.

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR^{14} or a -SR^{14} or -SC(=NH)NH_2 group respectively.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula $\text{-CO}_2\text{Alk}^7$ wherein Alk^7 is a group as defined hereinbefore.

When Alk^6 is present in or as a substituent it may be for example a methylene, ethylene, *n*-propylene, *i*-propylene, *n*-butylene, *i*-butylene, *s*-butylene, *t*-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S- , atoms or -S(O)- , $\text{-S(O)}_2\text{-}$ or $\text{-N(R}^9\text{)-}$ groups.

Cycloaliphatic or heterocycloaliphatic groups represented by the groups R^{13a} or R^{14} include those optionally substituted C_{3-10} cycloaliphatic or C_{3-10} heterocycloaliphatic groups described above for R^3 .

Aryl or heteroaryl groups represented by the groups R^{13a} or R^{14} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Ar^1 . The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet¹ or -Het² forms part of a substituent R¹³ each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally
 5 Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those R⁷ substituents described above.

Particularly useful atoms or groups represented by R¹³ include fluorine,
 10 chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, e.g. t-butyloxycarbonylpiperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl, oxazolidinyl, thiazolidinyl, imidazolidinyl or piperidinyl, C₁₋₆hydroxyalkyl,
 15 e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or
 20 pyridylthio, C₄₋₇cycloalkyl, e.g. cyclobutyl, cyclopentyl, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino or propylamino, C₆₋₁₂arylC₁₋₆alkylamino, e.g. benzylamino, 4-fluorobenzylamino or 4-hydroxyphenylethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g.
 25 aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, aminoC₁₋₆alkylamino, e.g. aminoethylamino or aminopropylamino, optionally substituted Het¹NC₁₋₆alkylamino, e.g. 3-morpholinopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g.
 30 aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino, e.g. 2-hydroxyethylamino, 3-hydroxypropylamino or 3-hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro,
 35 cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁷ [where Alk⁷ is as defined above], C₁₋₆alkanoyl e.g. acetyl,

propyryl or butyryl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl,
 e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), -SO₃Alk⁷,
 C₁₋₆alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl,
 C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propylsulphonyl,
 5 aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g.
 methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl C₁₋₆
 dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylamino-
 sulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆
 alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or
 10 propylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylamino-
 carbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g.
 aminoethylaminocarbonyl, C₁₋₆alkylaminoC₁₋₆alkylaminocarbonyl, e.g.
 methylaminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl,
 e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkyl-
 15 aminocarbonylamino, e.g. methylaminocarbonylamino or ethylamino-
 carbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylamino-
 carbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆
 alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonyl-
 amino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonyl-
 20 amino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonyl-
 amino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonyl-
 amino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonyl-
 methylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g.
 methylsulphonylamino or ethylsulphonylamino, haloC₁₋₆alkylsulphonyl-
 25 amino, e.g. trifluoromethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g.
 dimethylsulphonylamino or diethylsulphonylamino, optionally substituted
 phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkyl-
 aminosulphonylamino, e.g. methylaminosulphonylamino or ethylamino-
 sulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylamino-
 30 sulphonylamino or diethylaminosulphonylamino, optionally substituted
 morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino,
 optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g.
 acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆
 dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆
 35 alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆
 alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g.

methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R¹³ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R¹³ substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R³.

Where desired two R² substituents attached to a single carbon atom of the ring Cy may be linked together to form an optionally substituted spiro-linked monocyclic C₃₋₇cycloaliphatic or C₂₋₇heterocycloaliphatic group. C₃₋₇cycloaliphatic groups of this type include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl and cyclohexenyl groups. C₂₋₇heterocycloaliphatic groups include pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, and tetrahydrothiophenyl groups. Optional substituents which may be present on such groups include those optional substituents described hereinbefore in relation to R³ cycloaliphatic and heterocycloaliphatic groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates,

trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

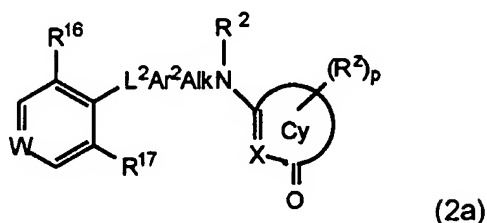
5 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

10 Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

15 In the compounds according to the invention the group R^1 is preferably an $Ar^1L^2Ar^2Alk$ - group. In compounds of this type Ar^1 is preferably an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic groups are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from
20 oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these Ar^1 groups include halogen atoms or alkyl, haloalkyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-CO_2H$, $-CO_2CH_3$, $-NO_2$, $-N(R^5)COR^6$ or $-CN$ groups as described above in relation to the
25 compounds of formula (1). Particularly useful bicyclic heteroaromatic groups represented by Ar^1 include optionally substituted ten-membered fused-ring heteroaromatic groups containing one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl and 2,7-
30 naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups. In compounds according to the invention the ring Cy is preferably an optionally substituted unsaturated cycloaliphatic or heterocycloaliphatic ring. One particularly useful class of
35 Cy rings is that in which m is the integer 1 and R^x represents an oxo substituent ($=O$) on a carbon atom adjoined to the group X. A further

particularly useful class of Cy rings is that in which m is zero, X is a C(R^w) group and the ring Cy contains an L⁷ sulfoxide or sulfone heteroatom containing group within its ring structure.

- 5 A particularly useful group of compounds according to the invention has the formula (2a):



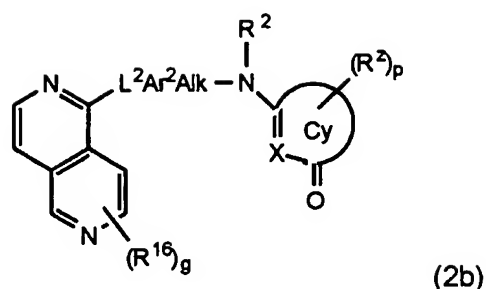
- 10 wherein -W= is -CH= or -N=;
 R¹⁶ and R¹⁷, which may be the same or different is each a hydrogen atom or an atom or group -L³(Alk²)_tL⁴(R⁴)_u in which L³, Alk², t, L⁴, R⁴ and u are as defined previously;
 L², Ar², Alk, R², Cy, X, R^z and p are as defined for formula (1);
 15 provided that Cy is other than a cyclobutenedione group;
 and the salts, solvates, hydrates and N-oxides thereof.

In one particularly useful class of compounds of formula (2a) -W= is a -N= atom.

- 20 In another particularly useful class of compounds of formula (2a) -W= is a -CH= group.

- R¹⁶ and R¹⁷ in compounds of formula (2a) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R¹⁶ and R¹⁷ substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially -CF₃, -CHF₂ or -CH₂F, methoxy or halomethoxy, especially -OCF₃, -OCHF₂ or -OCH₂F groups.

- 30 A further particularly useful group of compounds according to the invention has the formula (2b):



wherein R^{16} , L^2 , Ar^2 , Alk , Cy , R^2 , X , R^2 and p are as defined for formula (2a);

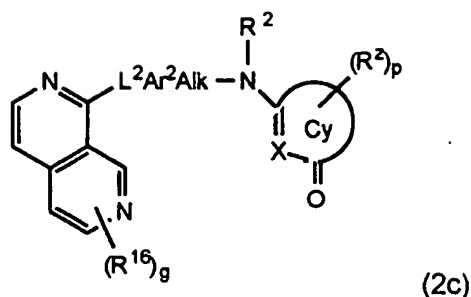
5 g is the integer 1, 2, 3 or 4.

provided that Cy is other than a cyclobutenedione group;
and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2b) may be
10 independently selected from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ in which
 L^2 , Alk^2 , t , L^3 , R^4 and u are as previously defined. Particularly useful R^{16}
substituents when present in compounds of formula (2b) include halogen
atoms, especially fluorine or chlorine atoms, or straight or branched C_{1-6} alkyl,
15 especially methyl, ethyl or isopropyl, C_{3-8} cycloalkyl especially cyclopropyl,
halo C_{1-6} alkyl, especially halomethyl, most especially $-CF_3$ or $-CHF_2$,
straight or branched C_{1-6} alkoxy, especially methoxy or ethoxy,
halo C_{1-6} alkoxy, especially halomethoxy, most especially $-OCF_3$ or
 $-OCHF_2$, $-SR^5$ especially methylthio or ethylthio, $-CN$, $-CO_2Alk^3$,
20 especially $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^5R^6$),
 $-N(R^5)COR^6$, especially $-NHCOCH_3$, $-COR^5$, especially $-COCH_3$,
optionally substituted C_{6-12} aromatic, especially optionally substituted
phenyl and C_{1-9} heteroaromatic groups, especially optionally substituted
thienyl, pyridyl and pyrimidinyl groups.

25 A further particularly useful group of compounds according to the invention
has the formula (2c):

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wherein R^{16} , g , L^2 , Ar^2 , Alk , Cy , R^2 , X , R^z and p are as defined for formula (2b);

- 5 provided that Cy is other than a cyclobutenedione group;
and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2d) may be independently selected from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ as
10 previously defined for compounds of formula (2b).

In one particularly preferred class of compounds of formula (2c) g is zero.

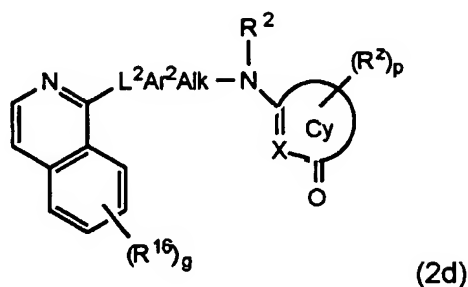
In another particularly preferred class of compounds of formula (2c) g is
15 the integer 1 or 2.

An especially preferred class of compounds of formula (2c) is that where g is the integer 1 and R^{16} is a substituent at the 3-position of the 2,7-naphthyridine ring. In this class of compounds R^{16} is most preferably a
20 methyl or halomethyl, especially $-CF_3$ group, or an optionally substituted phenyl group.

Particularly useful optional substituents which may be present on R^{16} aromatic and heteroaromatic groups when present in compounds of
25 formula (2b) or (2c) include halogen atoms, especially fluorine and chlorine atoms, C_{1-6} alkyl groups, especially fluorine and chlorine atoms, C_{1-6} alkyl groups, especially methyl, ethyl and i-propyl groups and $-CF_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCF_3$, $-SCH_3$, $-NHCH_3$, $-N(CH_3)_2$, $-CN$, $-CO_2CH_3$, $-COCH_3$, and $-N(CH_3)COCH_3$ groups.

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A further particularly useful group of compounds according to the invention has the formula (2d):



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wherein R^{16} , g , L^2 , Ar^2 , Alk , Cy , R^2 , X , R^2 and p are as defined for formula (2b);

provided that Cy is other than a cyclobutenedione group;
and the salts, solvates, hydrates and N-oxides thereof.

10

Each R^{16} atom or group in compounds of formula (2d) may be independently selected from an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$ as previously defined for compounds of formula (2b).

15 In one preferred class of compounds of formula (2d) g is zero.

In another preferred class of compounds of formula (2d) g is the integer 1. In this class of compounds R^{16} is preferably a substituent at the 3-positions of the isoquinoline ring as just defined. Most especially useful R^{16} substituents of this type include halogen atoms, especially fluorine and chlorine atoms and straight or branched C_{1-6} alkyl groups, especially methyl, ethyl or isopropyl, most especially methyl groups.

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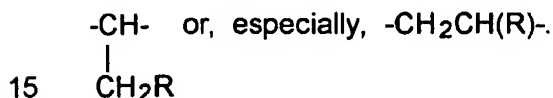
In another preferred class of compounds of formula (2d) g is the integer 2 or 3 where one R^{16} group is as just generally and particularly defined, and is located at the 3-position of the isoquinoline ring. In this class of compounds the second and when present third R^{16} optional substituents may be selected from an R^{16} optional substituent as described for compounds of formula (2b) or when g is the integer 3 a C_{1-6} alkylenedioxy group, especially a methylenedioxy or ethylenedioxy group. In one

30

particularly useful group of compounds of this class g is the integer 2 where one R^{16} group is at the 3-position of the isoquinoline ring as previously generally and particularly described and the other R^{16} group is at the 6-, 7- or 8-position of the isoquinoline ring, most especially the 7-position. Most especially preferred substituents at the 7-position include a halogen atom, especially a fluorine or chlorine atom, or a C_{1-6} alkoxy group, especially a methoxy group.

It will be understood that compounds according to formulae (2a), (2b), (2c) and (2d) include, where applicable, the corresponding hydroxy tautomers.

Alk in compounds of the invention is preferably:



In one preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) R^2 is a hydrogen atom.

In another preferred class of the compounds of formulae (1), (2a), (2b), (2c) and (2d) R is preferably a $-CO_2H$ group.

In a further preferred class of compounds of formulae (1) and (2) R is an esterified carboxyl group of formula $-CO_2Alk^7$. In this class of compound Alk^7 is preferably a C_{1-8} alkyl group, especially a methyl, ethyl, propyl or i-propyl group, an optionally substituted C_{6-10} aryl group, especially a phenyl group, an optionally substituted C_{6-10} aryl C_{1-6} alkyl group, especially a benzyl group, a C_{3-8} heterocycloalkyl C_{1-6} alkyl group, especially a morpholinyl-N-ethyl group or a C_{1-6} alkyloxy C_{1-6} alkyl group, especially a methoxyethyl group. Especially preferred esterified carboxyl groups include $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$ and $-CO_2CH(CH_3)_2$ groups.

In general in compounds of formula (2a) when W is a $-N=$ atom, L^2 is preferably L^{2a} where L^{2a} is a $-CON(R^8)-$ group, especially $-CONH-$ or

-(Alk^a)L^{2a}- where -(Alk^a)L^{2a}- is especially a -CH₂O- group. Most preferred is a -CONH- group.

5 In general in compounds of formula (2a) when W is a -CH= group L² is preferably a covalent bond or L^{2a} where L^{2a} is a -CON(R)⁸- group, especially -CONH- or -(Alk^a)L^{2a}- where -(Alk^a)L^{2a}- is especially a -CH₂O- group. When W in compounds of formula (2a) is a -CH= group L² is most preferably a covalent bond.

10 In general in compounds of formula (2b), (2c) and (2d) L² is preferably L^{2a} where L^{2a} is an -O- atom or -N(R⁸)- group. An especially useful -N(R⁸)- group is -NH-.

15 The group Ar² in compounds of formulae (1), (2a), (2b), (2c) and (2d) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

20 The ring Cy in compounds of formulae (1), (2a), (2b), (2c) and (2d) is preferably an optionally substituted cyclopentenyl, cyclohexenyl, cycloheptenyl, dihydropyrimidinyl, dihydropyridinyl or imidazolinyl group, each containing a oxo substituent (=O) within their ring structure on the carbon atom adjoined to the group X.

25 It will be understood that the corresponding hydroxy (-OH) tautomers of those oxo (=O) containing Cy rings, where the double bond migrates to become part of the Cy ring structure are also included in the definition or preferred Cy rings.

30 In one preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) the group X in the unsaturated heteroaliphatic ring represented by Cy is preferably a N atom. Preferred Cy rings containing this X group include optionally substituted 2-aminopyrimidin-4-ones [where amino refers to the group -N(R²)-], 4-aminopyrimidin-2-ones, 2-aminopyridin-4-ones, 6-aminopyridin-2-ones and 2-aminoimidazolin-4-ones.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) the group X in the unsaturated cycloaliphatic or heteroaliphatic ring represented by Cy is preferably a C(R^w) group. Particularly useful R^w atoms and groups that may be present in the group X include hydrogen and halogen atoms, especially fluorine, chlorine or bromine atoms or nitro, C₁₋₆alkyl, especially -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -(CH₂)₃CH₃, -CH(CH₃)₂, -C(CH₃)₃, -CH(CH₂CH₃)₂, -CH₂CH(CH₃)₂, and -CH₂C(CH₃)₃, C₂₋₆alkynylene, especially -CH₂CHCH₂ and -CH₂CH₂CHCH₂, C₂₋₆alkylnylene especially -CH₂CCH and -CH₂CH₂CCH, optionally substituted C₁₋₆alkylC₆₋₁₂aromatic, especially optionally substituted benzyl or phenylethyl, optionally substituted C₆₋₁₂aromatic, especially optionally substituted phenyl, optionally substituted C₃₋₁₀cycloaliphatic, especially optionally substituted C₃₋₇cycloalkyl, most especially optionally substituted cyclopentyl, cyclohexyl or cycloheptyl or optionally substituted C₃₋₁₀heterocycloaliphatic especially C₃₋₇heterocycloalkyl, most especially tetrahydropyranyl and tetrahydrothiopyranyl groups. Particularly preferred Cy rings in compounds of formulae (1), (2a), (2b), (2c) and (2d) containing such X groups include optionally substituted 3-amino-2-cyclopenten-1-one [where amino refers to the group -N(R²)-] and 3-amino-2-cyclohexen-1-one rings.

In general in compounds of formula (1), (2a), (2b), (2c) and (2d) p is preferably zero or the integer 1 or 2.

In one preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) p is zero or the integer 1 or 2. In this class of compounds Cy is preferably an optionally substituted 3-amino-2-cyclopenten-1-one ring. In one most preferred group of compounds of this class p is zero.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) p is zero or the integer 1 or 2. In this class of compounds Cy is preferably an optionally substituted 3-amino-2-cyclohexen-1-one ring.

In general in compounds of formulae (1), (2a), (2b), (2c) and (2d) when v and n in the group R^z are zero or the integer 1 the group R³ may especially be an optionally substituted heteroaliphatic, cycloaliphatic,

heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C₂₋₆heteroalkyl, particularly C₁₋₃alkoxyC₁₋₃alkyl, especially methoxypropyl, optionally substituted C₃₋₇cycloalkyl, especially optionally substituted cyclopropyl, cyclobutyl cyclopropyl or cyclohexyl, optionally substituted C₅₋₇heterocycloaliphatic, optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C₅₋₇heteroaromatic, especially optionally substituted pyridyl groups. Optional substituents on these groups include in particular R¹³ atoms or groups where the group is an aromatic or heteroaromatic group and -(L⁶)_p(Alk⁵)_qR¹² groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful -(L⁶)_p(Alk⁵)_qR¹² groups include those in which L⁶ is a -CO- group. Alk⁵ in these groups is preferably present (i.e. q is preferably an integer 1) and in particular is a -CH₂- chain. Compounds of this type in which R¹² is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) v is zero, Alk¹ in the group R² is present as an optionally substituted aliphatic chain as defined herein (i.e. n is the integer 1) and R³ is a hydrogen atom. Compounds of this type where -Alk¹R³ is an optionally substituted C₁₋₆alkyl group, particularly a methyl, ethyl, n-propyl, i-propyl, i-butyl, t-butyl or n-butyl group or an allyl (-CH₂CHCH₂) or (propargyl) -CH₂CCH group are especially useful. In one preferred group of compounds of this type L¹ is a covalent bond. In another preferred group of compounds of this type L¹ is a group -N(R⁸)- as previously generally and particularly defined.

Particularly preferred optional substituents which may be present on aliphatic groups of formula -Alk¹R³ include one, two, three or more halogen atoms, especially fluorine, chlorine or bromine atoms or C₁₋₆alkoxy groups e.g. methoxy or ethoxy, haloC₁₋₆alkoxy groups e.g. -OCF₃, substituted amino groups e.g. -NHCH₃ or -N(CH₃)₂ or -COR⁹ groups e.g.

-COCH₃ or carboxyl (-CO₂H) or esterified carboxyl e.g. -CO₂CH₃ or -CO₂C(CH₃)₂ groups.

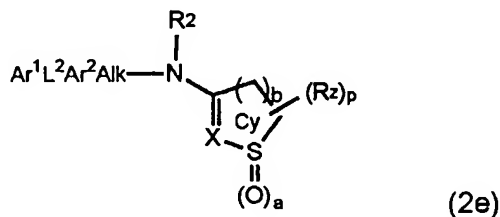
In one most preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) p is the integer 1 and R^z is an optionally substituted aliphatic group -Alk¹R³ as just defined.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) p is the integer 2 and R^z is an optionally substituted aliphatic group -Alk¹R³ as just defined. Most preferably the R^z groups are identical and especially preferred is the case where the R^z groups are each attached to the same carbon atom of the Cy ring.

In another preferred class of compounds of formulae (1), (2a), (2b), (2c) and (2d) p is the integer 2 and two R^z groups are joined to form a spiro-linked optionally substituted cycloaliphatic group (both R^z groups joined to a single carbon atom of Cy). Especially preferred optionally substituted cycloaliphatic groups of this type include spiro-fused cyclopentyl and cyclohexyl groups. Particularly preferred optional substituents which may be present on such groups include those just described in relation to -Alk¹R³.

A further particularly useful group of compounds according to the invention has the formula (2e):

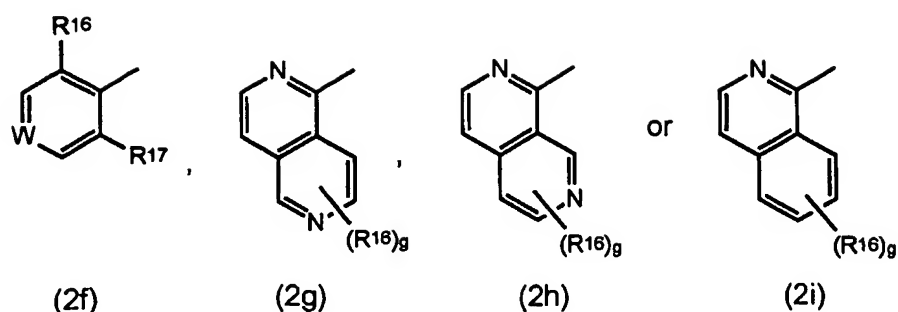
25



wherein:

Ar¹ is an aromatic or heteroaromatic group of formula

30



in which W, R¹⁶, R¹⁷ and g are as previously defined for formula (1);

a is the integer 1 or 2;

5 b is the integer 1, 2 or 3;

X is a group C(R^w);

and the salts, solvates, hydrates and N-oxides thereof.

10 In compounds of formula (2e) where Ar¹ is an aromatic group of formula (2f) W, R¹⁶, R¹⁷ and L² are in particular atoms or groups as particularly described in relation to compounds of formula (2a) hereinbefore.

15 In compounds of formula (2e) where Ar¹ is a heteroaromatic group of formula (2g), (2h) or (2i) R¹⁶, g and L² are in particular atoms or groups as particularly described in relation to compounds of formula (2b), (2c) and (2d) respectively.

In compounds of formula (2e), Ar², Alk, R² and R are in particular atoms or groups as particularly described in relation to compounds of formula (2a).

20 In one particularly preferred class of compounds of formula (2e) a is the integer 1.

25 In a most particularly preferred class of compounds of formula (2e) a is the integer 2.

In a further particularly preferred class of compound of formula (2e) b is the integer 1.

In compounds of formula (2e) R^w is preferably an atom or group as generally and particularly described hereinbefore in relation to compounds of formula (2a).

- 5 In one preferred class of compounds of formula (2e) p is the integer 1 and R^z is an aliphatic chain $-Alk^1R^3$ as particularly described in relation to compounds of formula (2a).

- 10 In another preferred class of compounds of formula (2e) p is the integer 2 and R^2 is an aliphatic chain $-Alk^1R^2$ or spiro-linked cycloaliphatic group as particularly described in relation to compounds of formula (2a).

Particularly useful compounds of the invention include:

- 15 (S)-3-[4-[(2,6-Naphthyridinyl)amino]phenyl]-2-[(2-(1-ethylpropyl)-3-oxo-1-cyclopentenyl)amino]propionic acid;
 (S)-3-[4-[(3-Methyl-2,7-naphthyridinyl)oxy]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
 (S)-3-[(4-[3-Methyl-2,7-naphthyridinyl]oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
 20 (S)-3-[(4-(2,7-Naphthyridin-1-yl)oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
 (S)-3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
 (S)-3-[4-[(3-Methyl-2,7-naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
 25 (S)-3-[4-(2',6'-Dimethoxy)biphenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
 (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate;
 30 (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isopropyl-3-oxo-1-cyclopentenyl)amino]propionic acid
 (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-allyl-3-oxo-1-cyclopentenyl)amino]propionate;
 (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionate;
 35

and the salts, solvates, hydrates and N-oxides and carboxylic acid ester, particularly methyl, ethyl, propyl and i-propyl esters thereof.

5 Compounds according to the invention are potent and selective inhibitors of $\alpha 4$ integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

10 The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders including inflammation in which the extravasulation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders,

15 Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

20 For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one
25 or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

30 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or
35 hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium

stearat , talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-

fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

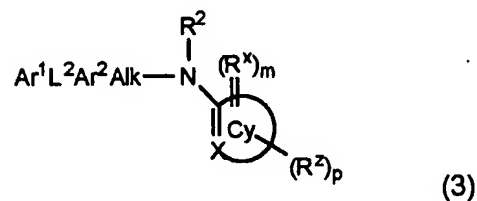
5 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

10 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral
15 administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

20 The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar^1 , Ar^2 , Alk, R^1 , R^2 , R^3 , L^1 , L^2 , Alk^1 , Cy, X, R^x , m, R^z , p, R^w and n when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise
25 indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example,
30 Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1999]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described
35 below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

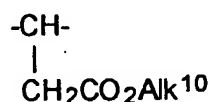
Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-\text{CO}_2\text{H}$ group may be obtained by hydrolysis of an ester of formula (3):

5



where Alk represents a group

10

$$-\text{CH}_2\text{CH}(\text{CO}_2\text{Alk}^{10})-, -\text{CH}=\text{CH}(\text{CO}_2\text{Alk}^{10})-, \text{ or}$$


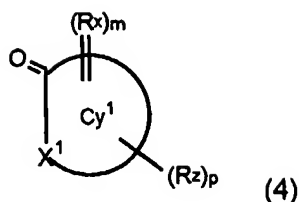
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[where Alk^{10} is an alkyl group, for example a C_{1-6} alkyl group]

The hydrolysis may be performed using either an acid or a base depending on the nature of Alk^{10} , for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

According to a further aspect of the invention a compound of formula (1) may be prepared by condensation of a compound of formula (4):

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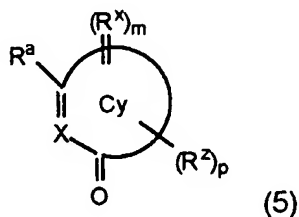


where Cy¹ is a cycloaliphatic or heterocycloaliphatic ring in which the double bond of the Cy ring of compounds of formula (1) is replaced by a single bond and an oxo (=O) substituent is attached to the carbon atom to which R¹R²N- will subsequently be joined and X¹ is a CH(R^w) or NH group, with an amine R¹R²NH or a salt thereof.

The reaction may be performed in an inert solvent or mixture of solvents, for example a hydrocarbon such as an aromatic hydrocarbon e.g. benzene or toluene and/or a halogenated hydrocarbon such as 1,2-dichloroethane, at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine R¹R²NH is used, an organic base such as diisopropylethylamine can be added.

Any carboxylic acid group present in the intermediate of formula (4) or the amine R¹R²NH may need to be protected during the displacement reaction, for example as an ethyl ester. The desired acid may then be obtained through subsequent hydrolysis, for example as particularly described above and generally described below.

A compound of formula (1) may also be prepared by displacement of a leaving group from a compound of formula (5):



where R^a is a leaving group, with an amine R¹R²NH or a salt thereof. Suitable leaving groups represented by R^a include a halogen atom

especially a chlorine, bromine or iodine atom, or alkoxy e.g. methoxy or ethoxy or isopropoxy, alkylthio e.g. methylthio or ethylthio, alkylsulphoxide e.g. methylsulphoxide, aryloxy e.g. dinitrophenyloxy or araalkoxy e.g. benzyloxy group.

5

The reaction may be performed in an inert solvent or mixture of solvents for example a substituted amide such as dimethylformamide, or alcohol such as methanol or ethanol and/or a halogenated hydrocarbon such as dichloromethane, at a temperature from 0°C to the reflux temperature.

10 Where necessary, for example when the salt of an amine R^1R^2NH is used an organic base such as diisopropylethylamine can be added.

Where desired the displacement reaction may also be performed on an intermediate of formulae (4) or (5) or R^1R^2NH which is linked, for example
15 via its R^1 or R^3 group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen.

20 Intermediates of formulae (4), (5) and R^1R^2NH may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation,
25 sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds.

30 Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^1H$ or $-L^2H$ group (where L^1 and L^2 is each a linker atom or group) may be treated with a coupling agent $R^3(Alk^1)_nX^1$ or Ar^1X^1 respectively in which X^1 is a leaving atom or group such as a
35 halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g.

trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

5 The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an
10 ether, e.g. a cyclic ether such as tetrahydrofuran.

Compounds of formula Ar^1X^1 may be prepared from alcohols of formula Ar^1OH by reaction with a halogenating agent, for example a phosphorous oxyhalide such as phosphorous oxychloride at an elevated temperature
15 e.g. 110°C.

Intermediate alcohols of formula Ar^1OH in which, for example, Ar^1 represents a 2,6-naphthyridine may be prepared by methods well known to a person skilled in the art, e.g. by the method of Sakamoto, T. *et al* [Chem.
20 Pharm. Bull. 33, 626-633, (1985)].

Alternatively alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,6-naphthyridine may be prepared by reaction of a 2,6-naphthyridine N-oxide or N, N'-dioxide with a halogenating agent, e.g. a
25 phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,5-dihalo-2,6-naphthyridine respectively. In the case of 1,5-dihalo-2,6-naphthyridines each halogen atom may be substituted separately by a reagent such as $HL^2Ar^2AlkN(R^2)H$ or $HL^3(Alk^2)_tL^4(R^4)_u$ by the particular methods just described above.

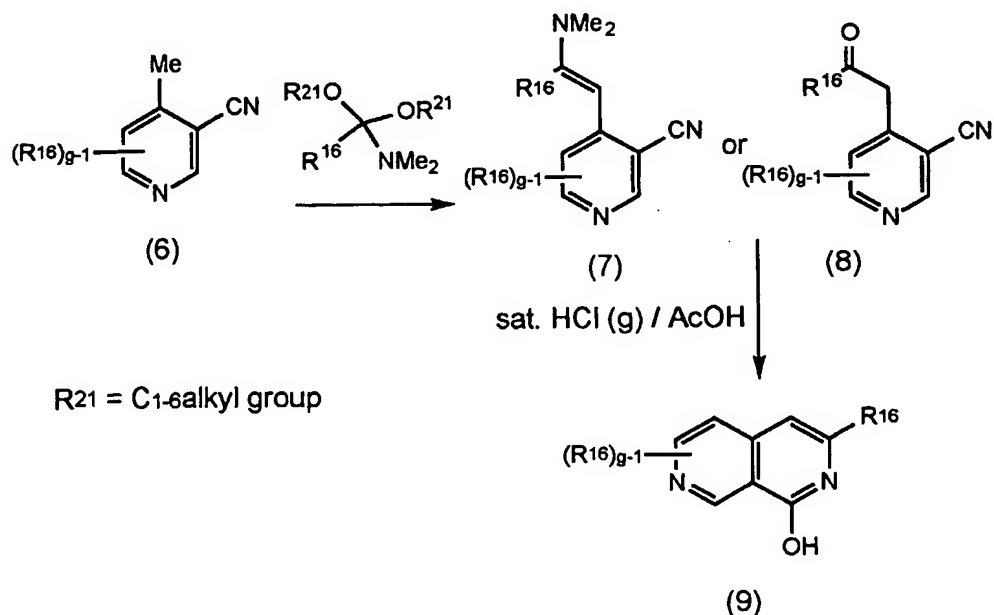
30 2,6-Naphthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,6-naphthyridines by the general methods of synthesis of N-oxides described below or they may be synthesised by the methods of Numata, A. *et al* (Synthesis, 1999, 306-311).

35

Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a 2,6-naphthyridine, may be prepared by the methods of Giacomello G. *et al* [Tetrahedron Letters, 1117-1121 (1965)], Tan, R. and Taurins, A. [Tetrahedron Lett., 2737-2744, (1965)], Ames, D. E. and Dodds, W. D. [J. Chem. Soc. Perkin 1, 705-710 (1972)] and Alhaique, F. *et al* [Tetrahedron Lett., 173-174 (1975)].

Intermediate alcohols of formula Ar¹OH in which Ar¹ represents an optionally substituted 2,7-naphthyridin-1-yl group may be prepared by methods well known to a person skilled in the art, e.g. by the method of Sakamoto, T. *et al* [Chem. Pharm. Bull. **33**, 626-633, (1985)] or Baldwin, J. J. *et al* [J. Org. Chem, **43**, 4878-4880, (1978)]. Thus for example the method of Baldwin may be modified to allow the synthesis of intermediate 3-substituted 2,7-naphthyridin-1-yl groups of formula Ar¹OH as depicted in Scheme 1:

Scheme 1



20

Reaction of an optionally substituted 4-methyl-3-cyano pyridine of formula (6) with a N,N-dimethylformamide di-C₁₋₆alkyl acetal, e.g. N,N-dimethylformamide diethyl acetal, in a dipolar solvent such as an amide e.g. a

substituted amide such as dimethylformamide at an elevated temperature e.g. 140-150° gives a compound of formula (7) or (8) or a mixture thereof depending on the nature of the group R¹⁶.

- 5 Compounds of formula (7) or (8) may be cyclised to 3-substituted 2,7-naphthyridin-1-yl alcohol of formula (9) by treatment with an acid e.g. an inorganic acid such as hydrochloric acid or hydrobromic acid or an acidic gas such as hydrogen chloride gas in an organic solvent e.g. an organic acid such as acetic acid optionally in the presence of water at a
10 temperature from about ambient to 50°C.

- Alternatively alkylating agents of formula Ar¹X¹ in which Ar¹ represents an optionally substituted 2,7-naphthyridin-yl group may be prepared by reaction of a 2,7-naphthyridine N-oxide or N, N'-dioxide with a
15 halogenating agent, e.g. a phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,6-dihalo- and/or-1,8-dihalo-2,7-naphthyridine respectively. In the case of 1,6-dihalo- and/or 1,8-dihalo-2,6-naphthyridines each halogen atom may be substituted separately by a reagent such as HL²Ar²AlkN(R²)H or HL³(Alk²)_tL⁴(R⁴)_u by the particular
20 methods just described above.

- 2,7-Naphthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,7-naphthyridines by the general methods of synthesis of N-oxides described below or they may be synthesised by the methods of
25 Numata, A. *et al* (Synthesis, 1999, 306-311).

- Further alkylating agents of formula Ar¹X¹ in which, for example, Ar¹ represents a 2,7-naphthyridin-1-yl, may be prepared by the methods of Wenkert E. *et al* J. Am. Chem. Soc. 89, 6741-5 (1967), and Aust. J. Chem.
30 433 (1972), and Sheffield D.J. J. Chem. Soc. Perkin. Trans I, 2506 (1972).

- Intermediate alcohols of formula Ar¹OH in which Ar¹ represents a 3-substituted isoquinolin-1-yl group may be prepared by methods well known to a person skilled in the art, e.g. by the methods of Wu M.-J. *et al* Tetrahedron, 55, 13193-200 (1999), Hiebl J. *et al* Tetrahedron Lett. 40,
35 7935-8 (1999), Nagarajan A. *et al* Indian J. Chem., Sect. B, 28B, 67-78

(1989), Brun E. M. *et al* Synlett, 7, 1088-90 (1999) and Brun, E. M. *et al* Synthesis, 273-280 (2000).

5 Further alkylating agents of formula Ar^1X^1 in which, for example, Ar^1 represents a isoquinolin-1-yl group, may be prepared by the methods of Falk H. *et al* Monatsch. Chem. 25, 325-33 (1994), and Deady, L. W. *et al* Aust. J. Chem 42, 1029-34 (1989).

10 In a further example intermediates of formula R^1R^2NH may be obtained by reaction of a compound of formula Ar^1L^2H with a compound of formula $X^1Ar^2AlkN(R^2)H$ under the reaction conditions just described

15 Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 2,6-naphthyridine and L^2 is a $-N(R^8)-$ group, may be prepared from substituted 4-cyano-3-cyanomethylpyridines by the methods of Alhaique, F. *et al* (*ibid* and Gazz. Chim. Ital. 1975, 105, 1001-1009) or from 3-formylpyridines by the methods of Molina, P. *et al* (Tetrahedron 1992, 48, 4601-4616).

20 Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 2,7-naphthyridin-1-yl group and L^2 is a $-N(R^8)-$ group, may be prepared from substituted 4-formylpyridines by the methods of Molina, P. *et al* Tetrahedron, 48, 4601-4616, (1992), or by the methods described in US 3,938,367.

25 Compounds of formula Ar^1L^2H in which, for example Ar^1 represents a 3-substituted isoquinolin-1-yl group and L^2 is a $-N(R^8)-$ group, may be prepared by the methods of Bordner, J. *et al* J. Med. Chem. 31, 1036-9 (1988), Tovar J. D. *et al* J. Org. Chem., 64, 6499-6504 (1999), Karser E. M. *et al* Synthesis, 11, 805-6 (1974), and Molino, P *et al* J. Chem. Soc. Perkin Trans. 1 1727-31 (1990).

30

In another example, compounds containing a $-L^1H$ or $-L^2H$ or group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $-C(S)X^2$, $-N(R^8)COX^2$ or $-N(R^8)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1 . The

35

reaction may be performed in the presence of a base, such as a hydrid ,
e.g. sodium hydride or an amine, e.g. triethylamine or N-methyl-
morpholine, in a solvent such as a halogenated hydrocarbon, e.g.
dichloromethane or carbon tetrachloride or an amide, e.g. dimethyl-
5 formamide, at for example ambient temperature. Alternatively, the
acylation may be carried out under the same conditions with an acid (for
example one of the alkylating agents described above in which X¹ is
replaced by a -CO₂H group) in the presence of a condensing agent, for
example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
10 or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a
catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as
1-hydroxybenzotriazole. Alternatively the acid may be reacted with a
chloroformate, for example ethylchloroformate, prior to the desired
acylation reaction

15
In a further example compounds may be obtained by sulphonylation of a
compound containing an -OH group by reaction with one of the above
alkylating agents but in which X¹ is replaced by a -S(O)Hal or -SO₂Hal
group [in which Hal is a halogen atom such as chlorine atom] in the
20 presence of a base, for example an inorganic base such as sodium
hydride in a solvent such as an amide, e.g. a substituted amide such as
dimethylformamide at for example ambient temperature.

25 In another example, compounds containing a -L¹H or -L²H group as
defined above may be coupled with one of the alkylation agents just
described but in which X¹ is replaced by an -OH group in a solvent such
as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine
and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

30 In a further example, ester groups -CO₂R⁵, -CO₂R¹¹ or -CO₂Alk⁷ in the
compounds may be converted to the corresponding acid [-CO₂H] by acid-
or base-catalysed hydrolysis depending on the nature of the groups R⁵,
R¹¹ or Alk⁷. Acid- or base-catalysed hydrolysis may be achieved for
example by treatment with an organic or inorganic acid, e.g. trifluoroacetic
35 acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a

solvent such as dioxan or an alkali metal hydroxide, .g. lithium hydroxid in an aqueous alcohol, e.g. aqueous methanol.

5 In a further example, $-OR^5$ or $-OR^{14}$ groups [where R^5 or R^{14} each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol $-OH$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around $-78^\circ C$.

10 Alcohol $[-OH]$ groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{14}$ group (where R^{14} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another
15 example, $-OH$ groups may be generated from the corresponding ester $[CO_2Alk^7$ or $CO_2R^5]$ or aldehyde $[-CHO]$ by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

20 In another example, alcohol $-OH$ groups in the compounds may be converted to a corresponding $-OR^5$ or $-OR^{14}$ group by coupling with a reagent R^5OH or $R^{14}OH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

25 Aminosulphonylamino $[-NHSO_2NHR^3$ or $-NHSO_2NHA r^1]$ groups in the compounds may be obtained, in another example, by reaction of a corresponding amine $[-NH_2]$ with a sulphamide $R^3NHSO_2NH_2$ or $Ar^1NHSO_2NH_2$ in the presence of an organic base such as pyridine at an
30 elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSAr^1$, $-CSNHA r^1$, $-NHCSR^3$ or $-CSNHR^3$ may be prepared by treating a corresponding compound containing a $-NHCOAr^1$, $-CONHA r^1$, $-NHCOR^3$ or $-CONHR^3$
35 group with a thiation reagent, such as Lawesson's Reagent, in an

anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

5 In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient
10 temperature.

In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient
15 temperature.

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support
20 such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

25 Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile;
30 a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L¹ or L² may be oxidised to the corresponding
35 sulfoxide or sulphone using an oxidising agent such as a peroxy acid,

e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In another example compounds of formula Ar^1X^1 (where X^1 is a halogen atom such as a chlorine, bromine or iodine atom) may be converted to such compounds as $\text{Ar}^1\text{CO}_2\text{R}^{20}$ (in which R^{20} is an optionally substituted alkyl, aryl or heteroaryl group), Ar^1CHO , $\text{Ar}^1\text{CHCHR}^{20}$, $\text{Ar}^1\text{CCR}^{20}$, $\text{Ar}^1\text{N}(\text{R}^{20})\text{H}$, $\text{Ar}^1\text{N}(\text{R}^{20})_2$, for use in the synthesis of for example compounds of formula $\text{Ar}^1\text{L}^2\text{Ar}^2\text{AlkN}(\text{R}^2)\text{H}$, using such well know and commonly used palladium mediated reaction conditions as are to be found in the general reference texts *Rodd's Chemistry of Carbon Compounds*, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-19 (John Wiley and Sons, 1999), *Comprehensive Heterocyclic Chemistry*, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Fleming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis*, Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's Comprehensive Organic Transformations* (VCH Publishers Inc., 1989) and *March's Advanced Organic Chemistry* (John Wiley and Sons, 1992).

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

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Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by
10 crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if
15 desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it
20 is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

25	NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
	MeOH - methanol;	BOC - butoxycarbonyl;
	DCM - dichloromethane;	AcOH - acetic acid;
	DIPEA - diisopropylethylamine;	EtOH - ethanol;
	Pyr - pyridine;	Ar - aryl;
	DMSO - dimethylsulphoxide;	iPr - isopropyl;
30	Et ₂ O - diethylether;	Me - methyl;
	THF - tetrahydrofuran,	DMF - N,N-dimethylformamide;
	Fmoc - 9-fluorenylmethoxycarbonyl;	
	DBU - 1,8-diazabicyclo[5,4,0]undec-7-ene	

35 All NMR's were obtained at 300MHz and 400MHz.

INTERMEDIATE 1**2-Benzyl-1.3-cyclopentanedione**

To a suspension of 1,3-cyclopentanedione (500mg, 5.10mmol) and anhydrous lithium iodide (750mg, 5.61mmol) in acetonitrile (10ml) was added DBU. After 30min benzyl bromide (1.74g, 10.2mmol) was added and the reaction heated for 24h at reflux. The reaction was poured into water (40ml), extracted with EtOAc (4 x 50ml), dried (MgSO₄), the solution concentrated *in vacuo* and the residue purified by chromatography (SiO₂; EtOAc) to give the title compound as an off white solid (222mg, 23%). δ H (CD₃OD) 7.20 (4H, d), 7.10 (1H, m), 3.41 (2H, s), 2.52 (4H, s). m/z (ESI, 70V) 189 (MH⁺).

INTERMEDIATE 2**2-Allyl-1.3-cyclopentanedione**

Prepared in a similar manner to Intermediate 1, from 1,3-cyclopentanedione and alkyl bromide, heating to reflux for 3 days to give the title compound as an refluxing for 3d with allyl bromide off-white solid (115mg, 8%). δ H (CD₃OD) 5.80 (1H, m), 5.00-4.80 (2H, 3 x m), 2.85 (2H, d), 2.48 (4H, s). m/z (ESI, 70V) 139 (MH⁺).

INTERMEDIATE 3**2-Butyl-1.3-cyclopentanedione**

To a suspension of cyclopent-4-ene-1,3-dione (1.22g, 12.6mmol) in acetic anhydride (4ml) were added ethyl orthobutyrate (3.74g, 25.3mmol) and anhydrous ZnCl₂. The reaction was heated at 80° for 24h, solid removed by filtration, the filtrate concentrated *in vacuo* and the residues purified by chromatography (SiO₂; 70:30 hexane/EtOAc) to give 2-(α -methoxypropylidene)cyclopent-4-ene-1,3-dione as a brown oil. δ H (CDCl₃) 6.88 (2H, s), 4.07 (3H, s), 3.00 (2H, t), 1.63 (2H, m), 1.08 (3H, t). m/z (ESI, 70V) 181 (MH⁺).

A solution of this oil (EtOH, 11ml) was subjected to catalytic (Pd/C, 200mg) hydrogenation for 24h, filtered, the solution concentrated *in vacuo*, and the residue purified by chromatography (SiO₂; EtOAc) to give the title compound as a white, waxy solid (494mg, 25%). δ H (CD₃OD) 2.46 (4H, s), 2.09 (2H, t, Δ 7.3Hz), 1.33 (4H, m), 0.89 (3H, t, Δ 9.5Hz). m/z (ESI, 70V) 155 (MH⁺).

INTERMEDIATE 4**2-Phenyl-1.3-Cyclopentanedione**

To a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (1.3g, 9.2mmol) and benzaldehyde diemethylacetal (1.0g, 6.6mmol) in DCM (5ml) under N_2 at -78° was added
5 a solution of 1,2-bis(trimethylsilyloxy)cyclobutene (1.4g, 6.1mmol) in DCM (3ml) maintaining a temperature of less than -70° . After 3h at -78°C the solution was poured into saturated NaHCO_3 solution (40ml), extracted into DCM, washed ($\text{NaHCO}_3 \times 1$, $\text{H}_2\text{O} \times 1$), dried (MgSO_4), the solution
10 concentrated *in vacuo* and the residue distilled (170° , 0.4mm Hg) to give 1.1g of clear liquid. To this liquid was added TFA (20ml) and the solution heated at reflux for 15 min. The solvent was removed *in vacuo*, the residue slurried in Et_2O and the off-white solids isolated by filtration and dried to give the title compound (760mg, 72%). δH (d^6 -DMSO) 7.80 (2H,
15 d, \downarrow 8.4Hz), 7.31 (2H, t), 7.16 (1H, t, \downarrow 7.35Hz), 2.51 (4H, s). m/z (ESI, 70V) 175 (MH^+).

INTERMEDIATE 5**2-Propyl-1.3-cyclopentanedione**

To a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (1.30g, 9.2mmol) and butyraldehyde (0.40g, 5.5mmol) in DCM (5ml) under N_2 at -78° was added a solution of 1,2-bis(trimethylsilyloxy)cyclobutene (1.4g, 6.1mmol) in DCM (3ml) maintaining a
20 temperature of less than -70° . After 2h at -78° the solution was poured into saturated NaHCO_3 , extracted into EtOAc, washed (brine), dried (MgSO_4) and the solution concentrated *in vacuo* to yield a clear liquid. To this liquid was added TFA (20ml) and the solution heated at reflux for 24h. The solution was concentrated *in vacuo* and the residue purified by chromatography (SiO_2 , 50:50 EtOAc/hexane) to yield the title compound as an off-white solid (140mg, 18%). δH (CD_3OD) 2.46 (4H, s), 2.07 (2H, t,
25 \downarrow 7.5Hz), 1.40 (2H, m), 0.86 (3H, t, \downarrow 7.4Hz). m/z (ESI, 70V) 141 (MH^+).

INTERMEDIATE 6**2-Isopropyl-1.3-cyclopentanedione**

To a solution of TiCl_4 (1.47g, 7.77mmol) and isobutyraldehyde (559mg, 7.75mmol) in DCM (16ml) under N_2 at -78° was added a solution of 1,2-bis(trimethylsilyloxy)cyclobutene (1.97g, 8.56mmol) in DCM (16ml)
35

maintaining a temperature of less than -70° . After 30min the reaction was poured into water, extracted into DCM, washed ($\text{H}_2\text{O} \times 2$), dried (MgSO_4) and the solution concentrated *in vacuo* to yield a clear oil. To this oil was added TFA (20ml) and the solution heated at reflux for 24h. The solution
5 was concentrated *in vacuo* and the residue purified by chromatography (SiO_2 ; 50:50 EtOAc/hexane) to give the title compound as an off-white solid (180mg, 17%). δH (d^6 -DMSO) 2.61 (1H, sept, \downarrow 7.0Hz), 2.29 (4H, s), 1.04 (6H, d, \downarrow 7.0Hz). m/z (ESI, 70V) 141 (MH^+).

10 INTERMEDIATE 7

2-Isobutyl-1,3-cyclopentanedione

To a stirring mixture of silica gel (45g) isobutyraldehyde (375mg, 5.20) and 4-methylbenzenethiol (3.80g, 30.6mmol) in DCM (15ml) was added 1,3-cyclopentanedione (300mg, 3.06mmol). The suspension was stirred for
15 24h, the solvent removed *in vacuo*, the residues dry packed onto the top of a silica column and the column run with gradient elution (SiO_2 ; 100:0 - 50:50 Hexane/EtOAc) to give a thiol trapped intermediate as a white solid (400mg, 47%). To this intermediate (300mg, 1.09mmol) in MeOH (5ml) was added NaCNBH_3 (55mg, 0.8mmol), the reaction stirred for 24h and
20 quenched with water. The solution was concentrated *in vacuo* and the residue purified by chromatography (SiO_2 ; 50:50, EtOAc/hexane) to give the title compound as an off-white solid (80mg, 28% overall). δH (CD_3OD) 2.43 (4H, s), 1.96 (2H, d, \downarrow 7.1Hz), 1.77 (1H, sept, \downarrow 6.6Hz), 0.83 (6H, d, \downarrow 6.6Hz). m/z (ESI, 70V) 155 (MH^+).

25

INTERMEDIATE 8

2-(1-Ethylpropyl)-1,3-cyclopentanedione

Prepared in a similar manner to intermediate 6 from 2-ethylbutyraldehyde δH (CD_3OD) 2.46 (4H, s), 2.30 (1H, m), 1.67 (2H, m), 1.52 (2H, m), 0.76
30 (6H, t, \downarrow 7.4Hz). m/z (ESI, 70V) 169 (MH^+).

INTERMEDIATE 9

2-Cyclohexyl-1,3-cyclopentanedione

To a suspension of 1,3-cyclopentanedione (4.00g, 0.040mmol) in water (30ml) were added $\text{LiOH} \cdot \text{H}_2\text{O}$ (1.88g, 0.045mol) and 3-bromocyclohexene (7.18g, 0.045mmol). The solution was stirred overnight, the pH raised to
35

12-14 (LiOH.H₂O) and stirred for 2h. The solution was washed with Et₂O (4 x 40ml), acidified to pH 1-2 and resulting solids isolated by filtration, washed and dried to give 2-cyclohexene-1,3-cyclopentanedione. [δ H (CD₃OD) 5.69 (1H, m), 5.44 (1H, m), 3.20 (1H, m), 2.47 (4H, s), 2.15-1.19 ~ (6H, m). m/z ESI, 70V) 179 (MH⁺)]. The product was dissolved in EtOH (50ml) and reduced under an atmosphere of H₂ at RT with Pd/C (200mg). After 5h the reaction was filtered and the solvent removed to give the title compound as a white solid (890mg 12%). δ H (CD₃OD) 2.44 (4H, 2), 2.39 (1H, m), 1.85-1.70 (5H, m), 1.50-1.45 (2H, m), 1.35-1.15 (3H, m). m/z (ESI, 70V) 181 (MH⁺).

INTERMEDIATE 10

4-(2-(N,N-Dimethylamino)ethylen-1-yl)-3-cyanopyridine

A solution of 4-methyl-3-cyanopyridine (prepared according to Ref: J. Prakt. Chem. 338, 663 (1996), 8.0g, 67.8mmol) and N,N-dimethylformamide diethyl acetal (11.0g, 74.8mmol) in dry DMF (50ml) was stirred at 140° under N₂ for 2 days. An additional portion of N,N-dimethylformamide diethyl acetal (5g) was added and stirred at 140° for 4h. The volatiles were removed *in vacuo* and the obtained dark oil partitioned between EtOAc (300ml) and water (50ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 100ml). The combined organic extracts were washed with brine (30ml), dried (Na₂SO₄), treated with activated charcoal, filtered and evaporated *in vacuo* to afford essentially pure title compound as a dull orange solid (10.1g, 85%). δ H (CDCl₃) 8.49 (1H, s), 8.25 (1h, d, \downarrow 5.9hz), 7.29 (1H, d, \downarrow 13.2Hz), 7.09 (1H, d, \downarrow 5.9Hz), 5.25 (1H, d, \downarrow 13.2Hz) and 2.99 (6H, s); m/z (ES⁺, 70V) 174 (MH⁺).

INTERMEDIATE 11

1-Hydroxy-2,7-naphthyridine hydrochloride salt

HCl gas was bubbled through a stirred solution of Intermediate 10 (6.2g, 3.58mmol) in glacial acetic acid (50ml) and water (0.64ml, 3.55mmol) for 1-2min. The reaction mixture was stirred in a stoppered flask at 40° for 18h. The volatiles were removed *in vacuo* affording a dark residue, which was treated with water (3 x 20ml) and re-evaporated *in vacuo*. The obtained dark semi-solid was treated with 40ml warm ethanol, ice-cooled,

and the undissolved solid collected by filtration affording the title compound as a green coloured solid (5.2g, 80%) δ H (DMSO-D₆) 12.5 (1H, br s), 9.38 (1H, s), 8.84 (1H, d, \downarrow 7.0Hz), 8.15 (1H, d, \downarrow 7.0Hz), 7.89 (1H, br dd, \downarrow 7.0, 5.0Hz) and 6.85 (1H, d, \downarrow 7.0Hz); m/z (ES⁺, 70V), 147 (MH⁺).

INTERMEDIATE 12

1-Chloro-2,7-naphthyridine

Intermediate 11 (5.2g, 28.5mmol) was stirred with phosphorous oxychloride (75ml) at 110° for 24h. The volatiles were removed *in vacuo* affording a dark oil which was poured into an ice-bath cooled mixture of saturated aqueous NaHCO₃ (100ml containing 20g solid NaHCO₃) and EtOAc (100ml). After thorough mixing the phases were separated and the aqueous layer re-extracted with EtOAc (2 x 75ml). The combined organic
15 extracts were washed with brine (15ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as a yellow solid (4.0g, 85%) δ H (CDCl₃) 9.45 (1H, s), 8.81 (1H, d, \downarrow 5.7Hz), 8.47 (1H, d, \downarrow 5.7Hz), 7.66 (1H, d, \downarrow 5.7Hz) and 7.60 (1H, d, \downarrow 5.7Hz); m/z (ES⁺, 70V) 165 and 167 (MH⁺).

20

INTERMEDIATE 13

Ethyl (S)-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]-2-amino propanoate

A solution of ethyl-(S)-3-[4-aminophenyl]-2-[*t*-butoxycarbonylamino] propanoate (638mg, 2.07mmol) and Intermediate 12 (310mg, 1.88mmol)
25 in ethoxyethanol (2ml) was stirred at 120° for 15 min and at 100° for 1h under nitrogen. The volatiles were removed *in vacuo* and the dark residue partitioned between EtOAc (70ml) and saturated aqueous NaHCO₃ (10ml). The phases were separated and the aqueous layer re-extracted
30 with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford a dark foam. Chromatography (SiO₂; 5 to 10% MeOH/DCM) afforded a mixture of ethyl-(S)-3-[4-(2,7-naphthyridin-1-ylamino)phenyl]-2-[(*t*-butoxycarbonyl) amino]propanoate and some of the title compound (730mg). This mixture
35 was treated with a solution of trifluoroacetic acid (5ml) and DCM (5ml) at room temperature for 1h. The volatiles were removed *in vacuo* and the

residue partitioned between EtOAc (75ml) and saturated aqueous NaHCO₃ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford an orange solid. Chromatography (silica; 10% MeOH/DCM) afforded the title compound as a straw-coloured solid (420mg, 60% over two steps). δ H (CDCl₃) 10.70 (1H, s), 10.31 (1H, s), 9.44 (1H, d, \downarrow 5.6Hz), 8.94 (1H, d, \downarrow 5.6Hz), 8.55 (1H, d, \downarrow 7.3Hz), 8.54 (2H, d, \downarrow 8.5Hz), 8.46 (1H, d, \downarrow 5.6Hz), 7.94 (2H, d, \downarrow 8.5Hz), 4.84 (2H, q, \downarrow 7.1Hz), 4.35 (1H, t, \downarrow 6.6Hz), 4.10 (2H, br s), 3.64 (1H, dd, \downarrow 13.5, 6.4Hz), 3.56 (1H, dd, \downarrow 13.5, 7.0Hz) and 1.95 (3H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 337 (MH⁺).

INTERMEDIATE 14

Ethyl (S)-3-[4-(2,7-naphthyridin-1-yloxy)phenyl]-2-aminopropanoate

A mixture of *N*-(BOC)-(S)-tyrosine ethyl ester (1.79g, 5.80 (mmol) potassium carbonate (0.80g, 5.80mmol) and Intermediate 12 (1.0g, 6.08mmol) in dry DMF (10ml) was stirred at room temperature for 18h, and at 40° for 18h. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (80ml) and 10% aqueous Na₂CO₃ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford a new colourless oil. Chromatography (silica; 2.5% MeOH/DCM) afforded reasonably pure *N*-t-butoxycarbonyl protected title compound (1.81g, 71%). This material was dissolved in EtOAc (40ml) and HCl gas was bubbled through the stirred solution for 1min. then the mixture was stirred for an additional 0.5h. The volatiles were removed *in vacuo* affording a yellow solid which was partitioned between EtOAc (80ml) and saturated aqueous NaHCO₃ (20ml). The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo*. The obtained oil was chromatographed (silica; 5% MeOH/DCM) to afford the title compound as a near colourless oil (0.87g, 62%) δ H (CDCl₃) 9.77 (1H, s), 8.75 (1H, d, \downarrow 5.8Hz), 8.10 (1H, d, \downarrow 5.8Hz), 7.58 (1H, d, \downarrow 5.8Hz), 7.29 (2H, d, \downarrow 8.4Hz), 7.25 (1H, d, \downarrow 5.9Hz), 7.21 (2H, d, \downarrow 8.4Hz), 4.22 (2H, q, \downarrow 7.1Hz), 3.80-3.70 (1H, obscured m), 3.15 (1H, dd, \downarrow 13.6, 5.1Hz), 2.88

(1H, dd, \downarrow 13.6, 8.0Hz) 1.30 (3H, t, \downarrow 7.1Hz) and 0.78 (2H, br s); m/z (ES⁺, 70V) 324 (MH⁺).

INTERMEDIATE 15

4-Acetyl-3-cyanopyridine

A solution of 4-methyl-3-cyanopyridine (4g, 33.9mmol) and *N,N*-dimethylacetamide dimethylacetyl (5.4g, 40.6mmol) in dry DMF (20ml) was stirred at 130° for 7h. The volatiles were removed *in vacuo* to afford a dark oil which solidified on standing. This material was chromatographed (silica; 50% EtOAc/ Hexane - 100% EtOAc) affording the title compound as an off-yellow solid (3.73g, 69%). δ H (CDCl₃) 8.87 (1H, s), 8.74 (1H, d, \downarrow 5.2Hz), 7.28 (1H, d, \downarrow 5.2Hz), 4.00 (2H, s) and 2.36 (3H, s); m/z (ES⁺, 70V) 161 (MH⁺).

INTERMEDIATE 16

1-Hydroxy-3-methyl-2,7-naphthyridine hydrochloride

HCl gas was bubbled through a stirred solution of Intermediate 15 (3.73g, 23.3mmol) in glacial acetic acid (40ml) for several minutes. The flask was stoppered and reaction stirred for 18h at ambient temperature. The volatiles were removed *in vacuo* affording a straw-coloured solid. This was twice treated with water (30ml portions) and re-evaporated *in vacuo* to dryness, affording the title compound (contaminated with ~25% unidentified by-product) as a dark straw coloured solid (4.1g). δ H (DMSO-*d*₆) 12.46 (1H, br s), 9.32 (1H, s), 8.71 (1H, d, \downarrow 6.5Hz), 7.98 (1H, d, \downarrow 6.5Hz), 6.67 (1H, s) and 2.38 (3H, s); m/z (ES⁺, 70V) 161 (MH⁺). Used without further purification.

INTERMEDIATE 17

1-Chloro-3-methyl-2,7-naphthyridine

Intermediate 16 (4.1g) was treated with phosphorus oxychloride (50ml) at 130° for 3h, affording a dark solution. The volatiles were removed *in vacuo* and the obtained dark oil extracted with Et₂O (100ml). Saturated aqueous NaHCO₃ (ice cold; containing 10g additional solid NaHCO₃) was poured (with CARE!) onto the crude product with swirling and ice-bath cooling. After thorough shaking, addition Et₂O (80ml) was added, the mixture re-shaken, and the phases separated. The aqueous layer was re-

extracted with Et₂O (2 x 80ml) and the combined ethereal extracts washed with brine (20ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford an orange solid (3.6g). Chromatography (silica; 70% EtOAc/Hexane - 100% EtOAc) afforded a more-polar by-product (3-methyl-1H-pyrano[3,4-C]pyridin-1-one, (0.7g) and the title compound as a white solid (2.82g, 79% from intermediate 7) δ H (CDCl₃) 9.66 (1H, s), 8.73 (1H, d, \downarrow 5.8Hz), 7.56 (1H, d, \downarrow 5.8Hz), 7.40 (1H, s) and 2.69 (3H, s); m/z (ES⁺, 70V) 179 and 181 (MH⁺).

10 INTERMEDIATE 18

Ethyl (S)-3-[4-(3-methyl-2,7-naphthyridin-1-ylamino)phenyl]-2-[N-(tert-butyloxycarbonyl)amino]propanoate hydrochloride

Acetylchloride (55mg, 50 μ l, 0.70mmol) was added to absolute ethanol (25ml) and stirred for one minute. Intermediate 17 (2.50g, 14.0mmol) and
15 ethyl-(S)-3-[4-aminophenyl]-2-{*tert*-butyloxycarbonyl}propanoate (4.31g, 14.0mmol) were added and the reaction mixture stirred at 60° for 2.75h. The volatiles were removed *in vacuo* to afford a yellow-orange solid. This was treated with EtOAc (~25ml), warmed, re-cooled and the precipitate collected by filtration, with Et₂O washing, affording the title compound as
20 yellow solid (4.96g, 73%). δ H (CDCl₃) 10.44 (1h, br s), 10.33 (1H, br s), 8.60 (1H, d, \downarrow 6.5Hz), 8.00 (1H, d, \downarrow 6.5Hz), 7.85 (2H, d, \downarrow 8.5Hz), 7.28 (1H, d, \downarrow 8.0Hz), 7.23 (2H, d, \downarrow 8.5Hz), 7.16 (1H, s), 4.19-4.01 (1H, m), 4.08 (2H, q, \downarrow 7.0Hz), 2.97 (1H, dd, \downarrow 13.8, 5.4 Hz), 2.86 (1H, dd, \downarrow 13.8, 10.0Hz), 2.50 (3H, s), 1.34 (9H, s) and 1.15 (3H, t, \downarrow 7.0Hz); m/z (ES⁺,
25 70V) 451 (MH⁺).

INTERMEDIATE 19

Ethyl-(S)-3-[4-(3-methyl-2,7-naphthyridin-1-ylamino)phenyl]-2-aminopropanoate

30 HCl gas was bubbled through a stirred solution of Intermediate 18 (4.95g, 10.2mmol) for 1-2min. After 30min stirring at ambient temperature the volatiles were removed *in vacuo* affording a yellow powder. This was treated with saturated aqueous NaHCO₃ (30ml) then extracted with EtOAc (100ml, and 3 x 50ml). The combined organic extracts were washed with
35 brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* affording the title compound as a yellow solid (3.56, 100%). δ H (CDCl₃) 9.25 (1H, s), 8.50

(1H, d, \downarrow 5.6Hz), 7.66 (2H, d, \downarrow 8.4Hz), 7.35 (1H, d, \downarrow 5.6Hz), 7.34 (1H, masked s), 7.14 (2H, d, \downarrow 8.4Hz), 6.81 (1H, s), 4.12 (2H, q, \downarrow 7.2Hz), 3.65 (1H, dd, \downarrow 7.8, 5.2Hz), 3.02 (1H, dd, \downarrow 13.7, 5.2Hz), 2.80 (1H, dd, \downarrow 13.7, 7.8Hz), 2.48 (3H, s), 1.56 (2H, br s) and 1.21 (3H, t, \downarrow 7.2Hz); m/z (ES⁺, 70V) 351 (MH⁺).

INTERMEDIATE 20

Ethyl (S)-3-[4-(3-methyl-2,7-naphthyridin-1-yloxy)phenyl]-2-(N-t-butyloxycarbonylamino)propanoate

10 A mixture of *N*-t-butyloxycarbonyl-(S)-tyrosine ethyl ester (14.5g, 46.9mmol), caesium carbonate (14.05g, 43.1mmol) and Intermediate 17 (7.0g, 39.2mmol) in dry DMF (60ml) was stirred at room temperature for 48h. The reaction was diluted with Et₂O (150ml) and filtered off. The filtrate was evaporated under high vacuum and the residue was
15 chromatographed (SiO₂; 40% - 60% EtOAc/Hexane) which afforded the title compound as a viscous, straw-coloured oil (16.2g, 77%) δ H (CDCl₃) 9.56 (1H, s), 8.58 (1H, d, \downarrow 5.8Hz), 7.39 (1H, d, \downarrow 5.8Hz), 7.15-7.10 (4H, m), 7.00 (1H, s), 4.99-4.91 (1H, m), 4.54-4.46 (1H, m), 4.09 (2H, q, \downarrow 7.1Hz), 3.10-2.99 (2H, m), 2.36 (3H, s), 1.34 (9H, s) and 1.15 (3H, t, \downarrow
20 7.1Hz); m/z (ES⁺, 70V) 452 (MH⁺).

INTERMEDIATE 21

Ethyl (S)-3-[4-(3-methyl-2,7-naphthyridin-1-yloxy)phenyl]-2-aminopropanoate

25 HCl gas was bubbled through a stirred solution of Intermediate 20 (16g) in EtOAc (300ml) until a persistent fine white precipitate formed (~2minutes). After stirring for 0.5h the volatiles were removed *in vacuo*. The obtained solid was partitioned between EtOAc (250ml) and saturated aqueous NaHCO₃ (80ml plus 5g solid NaHCO₃). The phases were separated and
30 the aqueous layer re-extracted with EtOAc (5 x 50ml). The combined organic extracts were washed with brine (10ml), dried (Na₂SO₄) and evaporated *in vacuo* to afford an oil. Chromatography (SiO₂; 100% EtOAc - 10% EtOH/EtOAc) afforded the title compound as a viscous oil (11.1g, 89%). δ H (CDCl₃) 9.71 (1H, s), 8.70 (1H, d, \downarrow 5.8Hz), 7.50 (1H, d, \downarrow
35 5.8Hz), 7.31-7.28 (4H, m), 7.11 (1H, s), 4.23 (2H, q, \downarrow 7.1Hz), 3.79-3.72 (1H, m), 3.14 (1H, dd, \downarrow 14.1, 5.4Hz), 2.94 (1H, dd, \downarrow 14.1, 7.8Hz), 2.47

(3H, s), 1.75-1.50 (2H, br s) and 1.30 (3H, t, \downarrow 7.1Hz); m/z (ES^+ , 70V) 352 (MH^+).

INTERMEDIATE 22

5 Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(4- [(trifluoromethylsulphonyloxy)phenyl]propanoate

Triflic anhydride (5.05ml, 30mmol) was added to a mixture of N-BOC tyrosine methyl ester (7.38g, 25mmol) and pyridine (10ml, 125mmol) in DCM (40ml) at 0°. After 45min at 0° water (80ml) and DCM (100ml) were
10 added. The organic phase was washed with NaOH aq. (0.5M, 60ml), water (60ml), citric acid (10%, 2 x 80ml) and water (60ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a yellow oil which solidified on standing (10.6g). δH ($CDCl_3$) 7.26-7.18 (4H, m), 5.05 (1H, v
br d), 4.59 (1H, v br q), 3.70 (3H, s), 3.16 (1H, dd, \downarrow 13.7, 5.7Hz), 3.02 (1H,
15 dd, \downarrow 13.8, 6.5Hz), 1.40 (9H, s); m/z (ES^+ , 70V) 450 (M^+ + Na).

INTERMEDIATE 23

Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(4-[2',6'-dimethoxy] biphenyl)propanoate

20 A mixture of the Intermediate 22 (4.27g, 10mmol), 2,6-dimethoxybenzene boronic acid (4.55g, 25mmol), potassium carbonate (6.9g, 50mmol) tetrakis(triphenylphosphine)palladium(0) (2.31g) in DME (45ml) and water (5ml) was heated at 80° overnight. The mixture was diluted with EtOAc, washed with dilute HCl, $NaHCO_3$ (aq.), water and brine, dried (Na_2SO_4)
25 and concentrated *in vacuo*. Column chromatography (SiO_2 ; EtOAc/hexane, 20:80 - 30:70) gave the title compound (2.27g). δH ($DMSO-d_6$) 7.33 (1H, d, \downarrow 8.2Hz), 7.27 (1H, t, \downarrow 8.3Hz), 7.20 (2H, d, \downarrow 8.1Hz), 7.10 (2H, d, \downarrow 8.0Hz), 6.71 (2H, d, \downarrow 8.4Hz), 4.2 (1H, m), 3.63 (9H, s), 3.01 (1H, dd, \downarrow 13.9, 4.5Hz), 2.84 (1H, dd, \downarrow 13.7, 10.3Hz), 1.34 (9H,
30 s); m/z (ES^+ , 70V) 438 (M^+ + Na).

INTERMEDIATE 24

Methyl (2S)-2-amino-3-(4-[2',6'-dimethoxy]biphenyl)propionate hydrochloride

35 Anhydrous HCl was bubbled through a solution of Intermediate 23 (1.30g, 3.13mmol) in EtOAc (30ml) for a few seconds. The mixture was stirred at

room temperature for 1h. Some solvent was removed *in vacuo* until material began to precipitate. The precipitate was filtered off and dried to give the title compound as pale yellow crystals (888mg, 81%). δ H (DMSO- d_6) 8.7 (2H, br s), 7.28 (1H, t, \downarrow 8.4Hz), 7.21 (2H, d, \downarrow 8.4Hz), 7.17 (2H, d, \downarrow 8.3Hz), 6.73 (2H, d, \downarrow 8.4Hz), 4.30 (1H, t, \downarrow 6.6Hz), 3.69 (3H, s), 3.64 (6H, s), 3.18 (1H, dd, \downarrow 14.1, 6.2Hz), 3.10 (1H, dd, \downarrow 14.1, 7.1Hz); m/z (ES $^+$, 70V) 316 (MH $^+$).

INTERMEDIATE 25

10 Ethyl N-(diphenylmethylene)-2-amino-3-(5-benzenesulphonyloxy-pyrid-2-yl)propionate

A solution of ethyl N-(diphenylmethylene)glycinate (1.71g, 6.40mmol) in dry THF (10ml) was added to a stirred solution of LDA (2M in heptane/TNF/ethylbenzene, 320ml, 6.40mmol) in dry THF 910ml) at -70 $^\circ$ under nitrogen. After stirring at this temperature for 0.75h, a solution of 5-benzenesulphonyloxy-2-bromomethylpyridine (2.00g, 6.01mmol); [prepared as described by Myers *et al*, J.O.C. 61, 813 (1996)] in dry THF (10ml) was added. The reaction mixture was stirred at -70 $^\circ$ for 1h then at room temperature for 18h. The reaction was quenched with water 910ml) then partitioned between EtOAc (70ml) and bring (30ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with brine (10ml), dried (Na $_2$ SO $_4$) and evaporated *in vacuo* to afford the crude product as a dark oil. Chromatography (silica: 60-75% Et $_2$ O/Hexane) afforded the title compound as a tan-coloured solid (2.25g, 72%). δ H (CDCl $_3$) 8.02 (1H, d, \downarrow 2.8Hz), 7.72 (2H, d, \downarrow 8.0hz), 7.59 (1H, t, \downarrow 8.0hz), 7.50 (2H, dd, \downarrow 8.4Hz), 7.40-7.27 (8H, m), 7.19 (1H, dd, \downarrow 8.5, 2.8Hz), 7.11 (1H, d, \downarrow 8.5Hz), 6.67 (2H, br d, \downarrow 8.0Hz), 4.50 (1H, dd, \downarrow 9.0, 4.6Hz), 4.25-4.10 (2H, m), 3.50-3.33 (2H, m) and 1.24 (3H, t, \downarrow 7.2Hz), m/z (ES $^+$, 70V) 515 (MH $^+$).

INTERMEDIATE 26

Ethyl 2-amino-3-(5-benzenesulphonyloxypyrid-2-yl)propionate

A solution of Intermediate 25 (1.9g, 3.7mmol) in 10% aqueous HCl (5ml) and ethanol (120ml) was stirred at room temperature for 1.5h. Most of the solvent was removed *in vacuo* and the residue partitioned between half-

saturated aqueous NaHCO₃ (50ml) and EtOAc (80ml). The phases were separated and the aqueous layer re-extracted with EtOAc (4 x 40ml). The combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo*. The obtained yellow oil was chromatographed (silica; EtOAc) to afford the title compound as a colourless oil (1.15g, 78%). δ H (CDCl₃) 8.04 (1H, d, \downarrow 2.8Hz), 7.80 (2H, d, \downarrow 8.0Hz), 7.65 (1H, t, \downarrow 8.0Hz), 7.51 (2H, t, \downarrow 8.0Hz), 7.31 (1H, dd, \downarrow 8.5, 2.8Hz), 7.12 (1H, d, \downarrow 8.5Hz), 4.10 (2H, q, \downarrow 7.1Hz), 3.86 (1H, dd, \downarrow 7.9, 4.9Hz), 3.19 (1H, dd, \downarrow 14.4, 4.9Hz), 2.99 (1H, dd, \downarrow 14.4, 7.9Hz), 1.66 (2H, br s) and 1.17 (3H, t, \downarrow 7.1Hz). m/z (ES⁺, 70V) 351 (MH⁺).

INTERMEDIATE 27

Ethyl-2-(N-*t*-butyloxycarbonylamino)-3-(5-hydroxypyrid-2-yl)propionate

15 A solution of Intermediate 26 (3.50g, 10mmol) and LiOH/H₂O (920mg, 22mmol) in dioxan (20ml) and water (30ml) was stirred at room temperature for 5h. The volatiles were removed *in vacuo* and the residue treated with ethanol (50ml). HCl gas was bubbled through the mixture for a few minutes and the reaction mixture heated at 50° overnight. The
20 volatiles were removed *in vacuo* and the residue treated with a mixture of di-*tert*-butyl dicarbonate (1.53g, 7.0mmol) and NaHCO₃ (3.36g, 40mmol) in THF (10ml) and water (20ml). After stirring at room temperature for 2h, additional di-*tert*-butyldicarbonate (150mg, 0.7mmol) was added, the reaction mixture stirred for a further 2h. The organic volatiles were
25 removed *in vacuo* and aqueous residue was extracted with EtOAc (2 x 75ml). The combined organic extracts were washed with brine (5ml), dried (MgSO₄) and evaporated *in vacuo*. The crude product was chromatographed (silica, 50% EtOAc/hexane) to afford the title compound as a white solid (1.81g, 58%), δ H (CDCl₃; 8:3 ratio of rotamers) 8.14
30 (0.73H, br s), 8.01 (0.27H, br s), 7.18-7.08 (1H, m), 7.08-6.90 (1H, m), 6.24 (0.27H, br dm \downarrow 8.5Hz), 5.77 (0.73H, br d \downarrow 8.5Hz), 4.64 (0.73H, m), 4.43 (0.27H, m), 4.17 (2H, q, \downarrow 7.1Hz), 3.27-3.14 (2H, m), 1.41 (9H, s and 1.23 (3H, t, \downarrow 7.1Hz). m/z (ES⁺, 70V) 311 (MH⁺).

INTERMEDIATE 28

Ethyl-2-(N-t-butyloxycarbonylamino)-3-[5-(3-methyl-2,7-naphthyridin-1-yloxy)-pyrid-2-yl]propionate

A mixture of intermediate 27 (1.814g, 5.85mmol), Intermediate 17 (0.87g, 4.87mmol) and Cs₂CO₃ (1.73g, 5.31mmol) in dry DMF (12ml) was stirred at 40° overnight. The inorganics were removed by filtration with DCM washed and the filtrate evaporated *in vacuo* to afford a dark oil. Chromatography (silica; 50% EtOAc/Hexane - 100% EtOAc) afforded the title compound as a white foam (1.69g, 77%). δH (CDCl₃) 9.71 (1H, s), 8.72 (1H, d, J 5.8Hz), 8.56 (1H, d, J 2.7Hz), 7.62 (1H, dd, J 8.4, 2.7Hz), 7.53 (1H, dd, J 5.8, 0.8Hz), 7.26 (1H, d, J 8.4Hz), 7.15 (1H, s), 5.86 (1H, br d, J 9.2Hz), 4.71 (1H, m), 4.81 (2H, m), 3.45-3.29 (2H, m), 1.46 (9H, s) and 1.27 (3H, t, J 7.2Hz); m/z (ES⁺, 70V) 453 (MH⁺).

INTERMEDIATE 29

Ethyl-2-amino-3-[5-(3-methyl-2,7-naphthyridin-1-yloxy)pyrid-2-yl]propionate

Intermediate 28 was dissolved in EtOAc and HCl gas bubbled through for 10min. Solution neutralised with aqueous NaHCO₃ and extracted into EtOAc to quantitatively give the title compound used crude without purification.

INTERMEDIATE 30

1,1-Dioxo-tetrahydrothiophen-3-one

Tetrahydrothiophen-3-one (2g, 19.6mmol) in CH₂Cl₂ (100ml) at 0° was treated with 3-chloroperoxybenzoic acid (9g) in CH₂Cl₂ (10ml). After 3h the reaction was complete and the solid removed by filtration and the filtrate concentrated *in vacuo*. The title compound was purified by chromatography (SiO₂; EtOAc/hexane 4:1) to give the title compound as a white solid (340mg; 2.5mmol; 13%). δH (CDCl₃) 3.72 (2H, s), 3.60 (2H, t, J 7.8Hz), 3.10 (2H, t, J 7.8Hz). m/z (ES⁺, 70V) 135 (MH⁺).

EXAMPLE 1

(2S)-Ethyl-3-[4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl]-2-[(3-oxo-1-cyclopentenyl)amino]propionate

A solution of (S)-ethyl-3-[4-(3,5-dichloropyrid-4-yl carboxamido)phenyl]-2-aminopropionate (prepared from 3,5-dichloroisonicotinoyl chloride and N-

BOC-L-4 aminophenylalanine ethylester) (128mg, 0.34mmol), and 1,3-cyclopentanedione (49mg, 0.50mmol) in chloroform (5ml) was treated with 4Å molecular sieves (~1g) and heated to reflux for 24h. The sieves were removed by filtration, the solution concentrated *in vacuo* and the residue purified by chromatography (SiO₂, gradient elution 98:2-96:4 DCM/MeOH) to give the title compound as a white solid (120mg, 77%). δH (CD₃OD) 8.61 (2H, s), 7.59 (2H, d, J 8.5Hz), 7.25 (2H, d, J 8.5Hz), 4.98 (1H, s), 4.33 (1H, t), 4.16 (2H, q, J 7.1Hz), 3.29-3.03 (2H, m), 2.63 (2H, m), 2.32 (2H, t, J 5.1Hz), 1.22 (3H, t, J 7.1Hz). m/z (ESI, 70V) 462 (MH⁺).

10

In a similar manner to Example 1 were prepared Examples 2 to 4.

EXAMPLE 2

(2S)-Ethyl-3-[4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl]-2-[(3-oxo-1-cyclohexenyl)amino]propionate

15

Prepared from 1,3-cyclohexanedione δH (CD₃OD) 8.62 (2H, s), 7.59 (2H, d, J 8.5Hz), 7.25 (2H, d, J 8.5Hz), 5.04 (1H, s), 4.35 (1H, t), 4.14 (2H, q, J 7.1Hz), 3.21-3.03 (2H, m), 2.43 (2H, m), 2.23 (2H, t, J 6.3Hz), 1.89 (2H, m), 1.19 (3H, t, J 7.1Hz). m/z (ESI, 70V) 476 (MH⁺).

20

EXAMPLE 3

(2S)-Ethyl-3-[4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from 2-ethyl-1,3-cyclopentanedione. Heated at reflux in 1,2-dichloro-ethane for 5 days. δH (CD₃OD) 8.62 (2H, s), 7.59 (2H, d, J 8.4Hz), 7.29 (2H, d, J 8.4Hz), 4.48 (1H, m), 4.22 (2H, q, J 7.1Hz), 3.32 (1H, dd, J 13.7, 4.6Hz), 3.06 (1H, dd, J 13.7, 9.8Hz), 2.5-2.0 (6H, m), 1.27 (3H, t, J 7.1Hz), 0.91 (3H, t, J 7.4Hz). m/z (ESI, 70V) 490 (MH⁺).

25

EXAMPLE 4

(2S)-Ethyl-3-[4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl]-2-[(5,5-dimethyl-3-oxo-1-cyclohexenyl)amino]propionate

Using 5,5-dimethyl-1,3-cyclohexanedione. Heated at reflux in 1,2-dichloroethane for 5 days (SiO₂, gradient 75:25 - 100:0 EtOAc/hexane). δH (CD₃OD) 8.64 (2H, s), 7.58 (2H, d, J 8.5Hz), 7.26 (2H, d, J 8.5Hz), 5.03 (1H, s), 4.36 (1H, m), 4.16 (2H, q, J 7.1Hz), 3.22 (1H, m), 3.05 (1H,

30

35

m), 2.29-2.11 (4H, m), 1.23 (3H, t, \downarrow 7.1Hz), 1.03 (3H, s), 0.97 (3H, s). m/z (ESI, 70V) 504 (MH^+).

EXAMPLE 5

5 **(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-methyl-3-oxo-1-cyclopentenyl)amino]propionate**

A solution of (S)-ethyl-3-(2,6-naphthyridin-1-yl) amino]phenyl]-2-amino propionate (prepared from 1-chloro-2,6-naphthyridine and N-BOC-L-4-aminophenylalanine ethyl ester as described in International Patent
10 Application WO 00/73260) (512mg, 1.52mmol) and 2-methyl-1,3-cyclopentanedione (179mg, 1.60mmol) in 1,2-dichloroethane (20ml) was treated with 4Å molecular sieves (0.5g) and heated at 90°C for 3 days. The solution was filtered, concentrated in *in vacuo* and the residue purified by chromatography (SiO₂, 98.2: 96.4 DCM/MeOH) to give the title compound
15 as a yellow solid (388mg, 59%). δH (CD₃OD) 9.13 (1H, s), 8.56 (1H, d, \downarrow 6.0Hz), 8.22 (1H, dt, \downarrow 6.0, 0.9Hz), 8.08 (1H, d, \downarrow 5.8Hz), 7.66 (2H, d, \downarrow 8.6Hz), 7.26 (2H, d, \downarrow 8.6Hz), 7.24 (1H, d, \downarrow 5.9Hz), 4.50 (1H, m), 4.24 (2H, q, \downarrow 7.1Hz), 3.30 (1H, m), 3.03 (1H, dd, \downarrow 13.7, 9.7Hz), 2.44 (1H, m), 2.30-2.05 (3H, m), 1.60 (3H, s), 1.29 (3H, t, \downarrow 7.1Hz). m/z (ESI, 70V) 431 (MH^+).
20

In a similar manner to Example 5 from (S)-ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-aminopropionate and the appropriate dione were prepared Examples 6-16.

25

EXAMPLE 6

(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from 2-ethyl-1,3-cyclopentanedione. δH (CD₃OD) 9.13 (1H, s),
30 8.57 (1H, d, \downarrow 5.9Hz), 8.22 (1H, d, \downarrow 6.0Hz), 8.08 (1H, d, \downarrow 5.8Hz), 7.67 (2H, d, \downarrow 8.5Hz), 7.26 (2H, d, \downarrow 8.5Hz), 7.25 (1H, d, \downarrow 5.0Hz), 4.48 (1H, m), 4.25 (2H, q, \downarrow 7.1Hz), 3.31 (1H, m), 3.05 (1H, m), 2.48 (1H, m), 2.25-2.05 (5H, m), 1.30 (3H, t, \downarrow 7.1Hz), 0.93 (3H, t, \downarrow 6.5Hz). m/z (ESI, 70V) 445 (MH^+).

35

EXAMPLE 7

(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-allyl-3-oxo-1-cyclohexenyl)amino]propionate

Prepared from 2-allyl-1,3-cyclohexanedione. δ H (CDI₃) 9.16 (1H, s), 8.62 (1H, d, \downarrow 5.9Hz), 8.20 (1H, d, \downarrow 5.6Hz), 7.88 (1H, d, \downarrow 5.8Hz), 7.73 (2H, d, \downarrow 8.3Hz), 7.18 (1H, d, \downarrow 5.8Hz), 7.12 (2H, d, \downarrow 8.3Hz), 5.68 (1H, m), 4.98 (2H, m), 4.36 (1H, m), 4.23 (2H, q, \downarrow 7.1Hz), 3.25-2.95 (4H, m), 2.40-1.70 (6H, 3xm), 1.30 (3H, t, \downarrow 7.1Hz). m/z (ESI, 70V) 471 (MH⁺).

EXAMPLE 8

10 **(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(5-phenyl-3-oxo-1-cyclohexenyl)amino]propionate**

Prepared from 5-phenyl-1,3-cyclohexanedione. δ H (CDI₃) 9.19 (1H, s), 8.70 (1H, 2xd \downarrow 5.8Hz), 8.16-8.15 (1H, 2x d, \downarrow 5.1Hz), 8.01 (1H, br), 7.66-7.61 (2H, 2 x d, \downarrow 8.4Hz), 7.35-7.05 (9H, m), 5.20 (1H, br), 4.24-4.22 (2H, 2 x q, \downarrow 7.1Hz), 3.34 (1H, m), 3.25 (1H, m), 3.05 (1H, m), 2.80-2.40 (4H, m), 1.32-1.30 (3H, 2 x t \downarrow 7.1Hz). m/z (ESI, 70V) 507 (MH⁺).

EXAMPLE 9

20 **(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(5-propyl-3-oxo-1-cyclohexenyl)amino]propionate**

Prepared from 5-propyl-1,3-cyclohexanedione 4Å sieves replaced with Na₂SO₄ (~1g) and acetic acid (1 drop). δ H (CD₃OD) 9.13 (1H, s), 8.57 (1H, d, \downarrow 6.0Hz), 8.23 (1H, d, \downarrow 6.0Hz), 8.09 (1H, d, \downarrow 5.8Hz), 7.68 (2H, d, \downarrow 8.4Hz), 7.24 (3H, m), 4.33 (1H, m), 4.16 (2H, m), 3.18 (1H, m), 3.05 (1H, m), 2.60-1.90 (3H, m), 1.35 (4H, br), 1.23-1.22 (3H, 2 x t, \downarrow 7.1Hz), 0.91 (3H, t). m/z (ESI, 70V) 473 (MH⁺).

EXAMPLE 10

30 **(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-benzyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediate 1. δ H (CD₃OD) 9.15 (1H, s), 8.59 (1H, d, \downarrow 6.0Hz), 8.24 (1H, d, \downarrow 6.0Hz), 8.12 (1H, d, \downarrow 5.8Hz), 7.62 (2H, d, \downarrow 8.4Hz), 7.30-7.00 (8H, m), 4.48 (1H, m), 4.21 (2H, q, \downarrow 7.0Hz), 3.52 (2H, m), 3.25 (1H, m), 2.95 (1H, m), 2.53 (1H, m), 2.30-2.05 (3H, m), 1.27 (3H, t, \downarrow 7.0Hz). m/z (ESI, 70V) 507 (MH⁺).

EXAMPLE 11**(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-allyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediate 2. δ H (CD₃OD) 9.14 (1H, s), 8.58 (1H, d, \downarrow 6.0Hz), 8.23 (1H, d, \downarrow 5.9Hz), 8.09 (1H, d, \downarrow 5.8Hz), 7.67 (2H, d, \downarrow 8.5Hz), 7.25 (1H, d, \downarrow 5.9Hz), 7.23 (2H, d, \downarrow 8.5Hz), 5.74 (1H, m), 5.00 (2H, m), 4.52 (1H, m), 4.24 (2H, q, \downarrow 7.1Hz), 3.30 (1H, m), 3.02 (1H, dd, \downarrow 13.8, 9.4Hz), 2.89 (2H, d, \downarrow 5.9Hz), 2.52 (1H, m), 2.30-2.05 (3H, m), 1.29 (3H, t, \downarrow 7.1Hz). m/z (ESI, 70V) 457 (MH⁺).

EXAMPLE 12**(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-butyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediate 3 4Å sieves replaced with Na₂SO₄ (~1g) and acetic acid (1 drop). δ H (CD₃OD) 9.14 (1H, s), 8.57 (1H, d, \downarrow 6.0Hz), 8.23 (1H, d, \downarrow 6.0Hz), 8.09 (1H, d, \downarrow 5.8Hz), 7.68 (2H, d, \downarrow 8.5Hz), 7.26 (2H, d, \downarrow 8.5Hz), 7.25 (1H, d), 4.50 (1H, dd), 4.25 (2H, q, \downarrow 7.1Hz), 3.31 (1H, m), 3.05 (1H, dd), 2.45 (1H, m), 2.25-2.05 (5H, m), 1.30 (7H, m) 0.89 (3H, t). m/z (ESI, 70V) 473 (MH⁺).

EXAMPLE 13**(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-phenyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediate 4. δ H (CD₃OD) 9.14 (1H, d, \downarrow 0.9Hz), 8.58 (1H, d, \downarrow 6.0Hz), 8.24 (1H, d, \downarrow 6.0Hz), 8.11 (1H, d, \downarrow 5.8Hz), 7.68 (2H, m), 7.39 (2H, m), 7.26 (5H, m), 4.52 (1H, m), 4.24 (2H, q), 3.30 (1H, m), 3.07 (1H, m), 2.60 (1H, m), 2.45-2.20 (3H, m), 1.30 (3H, t). m/z (ESI, 70V) 493 (MH⁺).

EXAMPLE 14**(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediate 5. δ H (CD₃OD) 9.10 (1H, d, \downarrow 0.8Hz), 8.55 (1H, d, \downarrow 6.0Hz), 8.20 (1H, d, \downarrow 6.0Hz), 8.07 (1H, d, \downarrow 5.8Hz), 7.66 (2H, d, \downarrow 8.5Hz), 7.24 (2H, d, \downarrow 8.5Hz), 7.21 (1H, d), 4.47 (1H, dd, \downarrow 9.8, 4.6Hz), 4.24 (2H, 1, \downarrow 7.1Hz), 3.29 (1H, m), 3.04 (1H, dd, \downarrow 13.8, 9.8Hz), 2.45 (1H,

m), 2.25-2.07 (5H, m), 1.36 (2H, m, \downarrow 7.5Hz), 1.29 (3H, t, \downarrow 7.1Hz), 0.87 (3H, t, \downarrow 7.3Hz). m/z (ESI, 70V), 459 (MH⁺).

EXAMPLE 15

5 **(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-isopropyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediate 6 4Å sieves replaced with Na₂SO₄ (~1g) and acetic acid (1 drop) (240mg, 41%). δ H (CD₃OD) 9.13 (1H, br), 8.55 (1H, br), 8.20 (1H, d), 8.09 (1H, d, \downarrow 5.8Hz), 7.68 (2H, d, \downarrow 8.6Hz), 7.24 (3H, d),
10 4.47 (1H, dd, \downarrow 9.3, 4.6Hz), 4.25 (2H, q, \downarrow 7.1Hz), 3.30 (1H, m), 3.07 (1H, dd, \downarrow 13.7, 9.3Hz), 2.70 (1H, sept, \downarrow 7.1Hz), 2.40 (1H, m), 2.25-2.05 (3H, m), 1.30 (3H, t, \downarrow 7.1Hz), 1.16 (3H, d, \downarrow 7.1Hz), 1.15 (3H, d, \downarrow 7.1Hz). m/z (ESI, 70V) 459 (MH⁺).

15 **EXAMPLE 16**

(2S)-Ethyl-3-[4-(2,6-naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from Intermediate 7, 4Å sieves replaced with Na₂SO₄ sieves (~1g) and acetic acid (1 drop) (50mg, 20%). δ H (CD₃OD) 9.12 (1H, d, \downarrow
20 0.8Hz), 8.57 (1H, d, \downarrow 6.0Hz), 8.22 (1H, d, \downarrow 6.0Hz), 8.08 (1H, d, \downarrow 5.8Hz), 7.67 (2H, d, \downarrow 8.5Hz), 7.24 (3H, d), 4.50 (1H, dd, \downarrow 9.6, 4.5Hz), 4.24 (2H, q, \downarrow 7.1Hz), 3.30 (1H, m), 3.05 (1H, dd, \downarrow 13.8, 9.7Hz), 2.43 (1H, m), 2.25-2.05 (3H, m), 1.98 (2H, d, \downarrow 14.6Hz), 1.74 (1H, sept), 1.29 (3H, t, \downarrow 7.1Hz), 0.84 (3H, d, \downarrow 6.6Hz), 0.83 (3H, d, \downarrow 6.6Hz). m/z (ESI, 70V) 473 (MH⁺).

25

EXAMPLE 17

(2S)-Ethyl-3-[4-(3-ethyl-isoquinolin-1-yl)amino]phenyl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionate

A solution of (S)-ethyl-3-[4-(3-ethyl-isoquinol-1-yl amino)phenyl]-2-aminopropionate [prepared from 1-chloro,3-ethyl-isoquinoline (from reaction of o-toluic acid with propionitrile and subsequent treatment with phosphorous oxychloride) and N-BOC-L-4-aminophenylalanine ethylester] (750mg, 2.07mmol) and 2-ethyl-1,3-cyclopentanedione (273mg, 2.17mmol) in 1,2-dichloroethane (10ml) was treated with 4Å sieves (~1g)
30 and heated at 90° for 3 days. The solution was filtered, concentrated *in vacuo* and the residue purified by chromatography (SiO₂, 100:1

DCM/MeOH) to give the title compound as a brown solid (511mg, 52%).
 δ H (d^6 -DMSO) 9.05 (1H, s), 8.46 (1H, d, \downarrow 7.0Hz), 7.91 (2H, d, \downarrow 8.6Hz),
7.72 (1H, d, \downarrow 7.0Hz), 7.64 (1H, t, \downarrow 7.0Hz), 7.51 (1H, t, \downarrow 7.0Hz), 7.23 (2H,
d, \downarrow 8.6Hz), 6.99 (1H, s), 4.32 (1H, m), 4.15 (2H, q, \downarrow 7.1Hz), 3.15 (1H, dd,
5 \downarrow 13.5, 3.5Hz), 3.01 (1H, dd, \downarrow 13.5, 9.6Hz), 2.69 (2H, t, \downarrow 7.5Hz), 2.29
(1H, m), 2.18 (1H, m), 2.06 (4H, m), 1.28 (3H, t, \downarrow 7.5Hz), 0.91 (3H, t, \downarrow
7.4Hz). m/z (ESI, 70V) 472 (MH^+).

EXAMPLE 18

10 **(2S)-3-[4-(3,5-Dichloropyrid-4-yl carboxamido)phenyl]-2-[(3-oxo-1-**
cyclopentenyl)amino]propionic acid

A solution of Example 1 (170mg, 0.37mmol) in THF (2ml) and water (2ml)
was treated with LiOH.H₂O (23mg, 0.55mmol) and stirred for 30 mins.
The mixture was concentrated *in vacuo* and purified by chromatography
15 (SiO₂, DCM:MeOH:AcOH:H₂O 200:20:3:2) to give the title compound as a
white solid (134mg, 84%). δ H (d^6 -DMSO) 10.72 (1H, br s), 8.65 (2H, s),
7.55 (1H, br s), 7.42 (2H, d, \downarrow 8.4Hz), 7.12 (2H, d, \downarrow 8.4Hz), 4.64 (1H, s),
3.92 (1H, br s), 2.94-2.81 (2H, m), 2.34 (2H, m), 1.97 (2H, t, \downarrow 5.5Hz).
 m/z (ESI, 70V) 434 (MH^+).

20

In a similar manner to Example 18 were prepared Examples 19-34:

EXAMPLE 19

25 **(2S)-3-[4-(3,5-Dichloropyrid-4-yl carboxamido)phenyl]-2-[(3-oxo-1-**
cyclohexenyl)amino]propionic acid

Prepared from Example 2. δ H (d^6 -DMSO) 10.95 (1H, br s), 8.90 (2H, s),
7.64 (2H, d, \downarrow 8.3Hz), 7.31 (2H, d, \downarrow 8.3Hz), 7.0 (1H, br s), 4.90 (1H, s),
3.97 (1H, br s), 3.15 (1H, dd, \downarrow 13.6, 5.5Hz), 3.06 (1H, dd, \downarrow 13.6, 6.8Hz),
2.43-2.17 (4H, m), 1.89 (2H, m). m/z (ESI, 70V) 448 (MH^+).

30

EXAMPLE 20

(2S)-3-[4-(3,5-Dichloropyrid-4-yl carboxamido)phenyl]-2-[(2-ethyl-3-
oxo-1-cyclopentenyl)amino]propionic acid

Prepared from Example 3. δ H (d^6 -DMSO) 10.86 (1H, s), 8.79 (2H, s),
35 7.55 (2H, d, \downarrow 8.3Hz), 7.31 (2H, d, \downarrow 8.3Hz), 7.08 (1H, d, \downarrow 9.1Hz), 4.26
(1H, m), 3.17 (1H, dd, \downarrow 13.5, 4.2Hz), 3.01 (1H, dd, \downarrow 13.5, 9.9Hz), 2.31

(1H, dd, \downarrow 13.1, 5.0Hz), 2.10-1.90 (5H, m), 0.81 (3H, t, \downarrow 7.4Hz). m/z (ESI, 70V) 462 (MH^+).

EXAMPLE 21

5 **(2S)-3-[4-(3,5-Dichloropyrid-4-ylcarboxamido)phenyl]-2-[(5,5-dimethyl-3-oxo-1-cyclohexenyl)amino] propionic acid**

Prepared from Example 4. δH (d^6 -DMSO) 10.48 (1H, s), 8.70 (2H, s), 7.55 (2H, d, \downarrow 7.7Hz), 7.26 (2H, d, \downarrow 7.7Hz), 4.87 (1H, s), 4.12 (1H, s), 3.13 (1H, dd, \downarrow 13.9, 5.8Hz), 3.01 (1H, dd, \downarrow 13.9, 7.6Hz), 2.21 (2H, m), 1.97 (2H, s), 0.99 (3H, s), 0.96 (3H, s). m/z (ESI, 70V) 476 (MH^+).

EXAMPLE 22

15 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-methyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 5. δH (d^6 -DMSO) 9.28 (1H, s), 9.21 (1H, s), 8.66 (1H, d, \downarrow 5.9Hz), 8.40 (1H, dd, \downarrow 6.0, 0.8Hz), 8.13 (1H, d, \downarrow 5.7Hz), 7.71 (2H, d, \downarrow 8.5Hz), 7.25 (1H, d, \downarrow 5.7Hz), 7.15 (2H, d, \downarrow 8.5Hz), 6.56 (1H, d, \downarrow 8.1Hz), 3.78 (1H, m), 3.11 (1H, d), 2.85 (1H, dd, \downarrow 13.3, 8.0Hz), 2.31 (1H, m), 2.00-1.75 (3H, m), 1.44 (3H, s). m/z (ESI, 70V) 403 (MH^+).

EXAMPLE 23

20 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 6. δH (d^6 -DMSO) 9.30 (1H, s), 9.22 (1H, s), 8.67 (1H, d), 8.39 (1H, d), 8.14 (1H, d), 7.78 (2H, m), 7.28 (3H, m), 7.10 (1H, d), 4.28 (1H, m), 3.18 (1H, dd, \downarrow 13.6, 4.3Hz), 3.01 (1H, dd, \downarrow 13.6, 10.0Hz), 2.40-1.90 (6H, m), 0.83 (3H, t, \downarrow 7.4Hz). m/z (ESI, 70V) 417 (MH^+).

EXAMPLE 24

30 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-allyl-3-oxo-1-cyclohexenyl)amino]propionic acid**

Prepared from Example 7. δH (d^6 -DMSO) 9.31 (1H, s), 9.23 (1H, s), 8.68 (1H, d, \downarrow 5.9Hz), 8.41 (1H, d, \downarrow 5.8Hz), 8.14 (1H, d, \downarrow 5.7Hz), 7.80 (2H, m), 7.28 (1H, d, \downarrow 5.7Hz), 7.18 (2H, d, \downarrow 8.5Hz), 5.77 (1H, d, \downarrow 8.7Hz), 5.57 (1H, m), 4.93 (1H, dd, \downarrow 17.2, 1.8Hz), 4.85 (1H, dd, \downarrow 10.0, 1.8Hz), 4.42 (1H, br), 3.11 (1H, dd, \downarrow 13.7, 4.7Hz), 3.07 (1H, dd, \downarrow 13.7, 8.0Hz), 2.95

(2H, d, \downarrow 5.6Hz), 2.31 (1H, m), 2.14 (1H, m), 2.06 (2H, m), 1.69 (2H, m).
 m/z (ESI, 70V) 443 (MH^+).

EXAMPLE 25

5 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(5-phenyl-3-oxo-1-cyclohexenyl)amino]propionic acid**

Prepared from Example 8. δH (d^6 -DMSO) 9.33 (1H, s), 9.23 (1H, s), 8.69 (1H, d, \downarrow 5.8Hz), 8.41 (1H, d, \downarrow 5.8Hz), 8.15 (1H, d, \downarrow 5.6Hz), 7.32-7.20 (9H, m), 4.89 (1H, s), 4.10 (1H, m), 3.20 (2H, m), 3.09 (1H, dd, \downarrow 13.7, 5.2Hz), 2.99 (1H, m), 2.72-2.23 (4H, m). m/z (ESI, 70V) 479 (MH^+).

EXAMPLE 26

15 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(5-propyl-3-oxo-1-cyclohexenyl)amino]propionic acid**

Prepared from Example 9. δH (d^6 -DMSO) 9.40 (1H, d, \downarrow 0.7Hz), 9.30 (1H, s), 8.86 (1H, d, \downarrow 5.9 Hz), 8.56 (1H, d, \downarrow 5.9Hz), 8.35 (1H, d, \downarrow 5.7Hz), 7.99 (2H, d, \downarrow 8.3Hz), 7.43 (3H, m), 6.95 (1H, d, \downarrow 7.4Hz), 4.31 (1H, m), 3.31 (1H, m), 3.16 (1H, m), 2.64 (1H, dt, \downarrow 15.5, 3.7Hz), 2.37-2.00 (4H, m), 1.51 (4H, m), 1.08 (3H, dt, \downarrow 6.8, 1.9Hz). m/z (ESI, 70V) 445 (MH^+).

EXAMPLE 27

20 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-benzyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 10. δH (d^6 -DMSO) 9.30 (1H, s), 9.23 (1H, s), 8.68 (1H, d, \downarrow 5.9Hz), 8.41 (1H, d, \downarrow 5.9Hz), 8.16 (1H, d, \downarrow 5.7Hz), 7.76 (2H, d), 7.29 (1H, d, \downarrow 5.8Hz), 7.23-7.10 (6H, m), 7.09 (1H, m), 4.17 (1H, br), 3.39 (2H, m), 3.16 (1H, br d), 2.94 (1H, br d), 2.39 (1H, dd, \downarrow 16.3, 7.0Hz), 2.15-1.92 (3H, m). m/z (ESI, 70V) 479 (MH^+).

EXAMPLE 28

30 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-allyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 11. δH (d^6 -DMSO) 9.29 (1H, s), 9.22 (1H, s), 8.67 (1H, d, \downarrow 5.9Hz), 8.39 (1H, d, \downarrow 5.9Hz), 8.13 (1H, d, \downarrow 5.7Hz), 7.76 (2H, m), 7.27 (1H, d, \downarrow 5.7Hz), 7.22 (2H, d, \downarrow 8.5Hz), 6.93 (1H, br), 5.69 (1H, m), 4.93 (1H, d, \downarrow 16.8Hz), 4.86 (1H, dd, \downarrow 10.0, 2.0Hz), 4.22 (1H, br),

3.14 (1H, dd, \downarrow 13.8, 4.3Hz), 2.96 (1H, m), 2.78 (2H, d, \downarrow 4.3Hz), 2.36 (1H, dd, \downarrow 16.8, 7.1Hz), 2.10-1.90 (3H, m). m/z (ESI, 70V) 429 (MH^+).

EXAMPLE 29

5 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-butyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 12. δH (d^6 -DMSO) 9.29 (1H, s), 9.22 (1H, s), 8.68 (1H, d, \downarrow 5.9Hz), 8.40 (1H, dd, \downarrow 5.9, 1.0Hz), 8.14 (1H, dd, \downarrow 5.7, 1.3Hz), 7.79 (2H, d, \downarrow 8.5Hz), 7.26 (3H, m), 6.97 (1H, br), 4.25 (1H, m),
10 3.17 (1H, dd, \downarrow 13.6, 3.9Hz), 3.00 (1H, dd, \downarrow 13.0, 10.0Hz), 2.32 (1H, m), 2.20-1.95 (5H, m), 1.21 (4H, m), 0.85 (3H, t, \downarrow 6.9Hz). m/z (ESI, 70V) 445 (MH^+).

EXAMPLE 30

15 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-phenyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 13. δH (d^6 -DMSO) 9.30 (1H, br), 9.23 (1H, d, \downarrow 0.6Hz), 8.68 (1H, d, \downarrow 5.9Hz), 8.39 (1H, d, \downarrow 5.9Hz), 8.13 (1H, d, \downarrow 5.8Hz), 7.80 (2H, d, \downarrow 8.5Hz), 7.38-7.18 (8H, m), 6.70 (1H, d, \downarrow 8.9Hz), 4.49 (1H, m),
20 m), 3.17 (1H, m), 3.10 (1H, m), 2.59 (1H, m), 2.43 (1H, m), 2.25 (1H, m). m/z (ESI, 70V) 465 (MH^+).

EXAMPLE 31

25 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 14. δH (d^6 -DMSO) 9.29 (1H, s), 9.22 (1H, s), 8.68 (1H, d, \downarrow 5.9Hz), 8.39 (1H, dd, \downarrow 5.9, 0.9Hz), 8.14 (1H, dd, \downarrow 5.6, 1.3Hz), 7.78 (2H, m), 7.27 (3H, m), 7.05 (1H, d, \downarrow 9.4Hz), 4.28 (1H, m), 3.18 (1H, dd, \downarrow 13.6, 4.3Hz), 2.97 (1H, dd, \downarrow 13.6, 9.9Hz), 2.33 (1H, m),
30 2.15-2.05 (5H, m), 1.26 (2H, hex, \downarrow 7.1Hz), 0.82 (3H, t, \downarrow 7.3Hz). m/z (ESI, 70V) 431 (MH^+).

EXAMPLE 32

35 **(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isopropyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 15. δ H (d^6 -DMSO) 9.30 (1H, s), 9.23 (1H, s), 8.68 (1H, br), 8.40 (1H, d, \downarrow 5.7Hz), 8.14 (1H, d, \downarrow 5.7Hz), 7.79 (2H, m), 7.25 (3H, m), 6.79 (1H, d, \downarrow 9.4Hz), 4.29 (1H, m), 3.17 (1H, dd, \downarrow 13.6, 4.4Hz), 3.04 (1H, dd, \downarrow 13.5, 9.6Hz), 2.69 (1H, sept, \downarrow 7.0Hz), 2.27 (1H, m), 2.05-1.85 (3H, m), 1.09 (3H, d, \downarrow 7.1Hz), 1.06 (3H, d, \downarrow 7.1Hz). m/z (ESI, 70V) 431 (MH^+).

EXAMPLE 33**(2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 16. δ H (d^6 -DMSO) 9.29 (1H, s), 9.22 (1H, s), 8.67 (1H, d, \downarrow 5.9Hz), 8.40 (1H, d, \downarrow 5.9Hz), 8.13 (1H, d, \downarrow 5.7Hz), 7.78 (2H, d, \downarrow 8.5Hz), 7.24 (3H, m), 6.89 (1H, d, \downarrow 9.2Hz), 4.22 (1H, m), 3.17 (1H, dd, \downarrow 13.6, 4.2Hz), 2.99 (1H, dd, \downarrow 13.4, 9.6Hz), 2.33 (1H, m), 2.07-1.88 (5H, m), 1.67 (1H, sept, \downarrow 6.6Hz), 0.78 (3H, d, \downarrow 6.6Hz), 0.77 (3H, d, \downarrow 6.6Hz). m/z (ESI, 70V) 445 (MH^+).

EXAMPLE 34**(2S)-3-[4-(3-Ethylisoquinolin-1-yl)amino]phenyl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 17. δ H (d^6 -DMSO) 9.04 (1H, s), 8.46 (1H, d, \downarrow 7.1Hz), 7.87 (2H, d, \downarrow 8.5Hz), 7.71 (1H, d, \downarrow 7.1Hz), 7.64 (1H, t, \downarrow 7.1Hz), 7.51 (1H, t, \downarrow 7.1Hz), 7.23 (2H, d, \downarrow 8.6Hz), 7.07 (1H, d, \downarrow 9.2Hz), 6.98 (1H, s), 4.28 (1H, m), 3.16 (1H, dd, \downarrow 13.6, 4.3Hz), 3.00 (1H, dd, \downarrow 13.6, 9.9Hz), 2.69 (2H, q, \downarrow 7.5Hz), 2.33 (1H, m), 2.06 (5H, m), 1.28 (3H, t, \downarrow 7.5 Hz), 0.84 (3H, t, \downarrow 7.3Hz). m/z (ESI, 70V) 444 (MH^+).

EXAMPLE 35**(S)-Ethyl-3-[4-[(2,7-Naphthyridin-1-yl)oxy]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amiono]propionate**

A solution of Intermediate 21 (355mg, 1.01mmol) and Intermediate 5 (156mg, 1.11mmol) in nitromethane (5ml) with Na_2SO_4 (~0.5g) and acetic acid (2 drops) was heated for 2 days at 90°. The solution was filtered, filtrate concentrated *in vacuo* and residue purified by silica chromatography (SiO_2 ; 0.4% MeOH in DCM) to give the title compound as an off white solid (222mg 46%). δ H (DMSO) 9.43 (1H, s), 8.56 (1H, d, \downarrow

5.7Hz), 7.59 (1H, d, \downarrow 5.8Hz), 7.23 (1H, s), 7.20 (2H, d, \downarrow 8.3Hz), 7.06 (2H, d, \downarrow 8.4Hz), 7.05 (1H, d), 4.28 (1H, m), 3.99 (2H, q, \downarrow 7.1Hz), 3.07 (1H, dd, \downarrow 13.6, 5.2Hz), 2.94 (1H, dd, \downarrow 13.5, 9.8Hz), 2.19 (3H, s), 2.20-1.84 (6H, m), 1.09 (2H, m), 1.03 (3H, t, \downarrow 7.1Hz), 0.64 (3H, t, \downarrow 4.7Hz). m/z (ESI, 70V) 474 (MH⁺).

In a similar manner to Example 35 were prepared Examples 36 to 48

EXAMPLE 36

10 **(S)-Ethyl-3-[(4-(2,6-naphthyridin-1-yl)amino)phenyl]-2-[(1-ethylpropyl)-3-oxo-1-cyclopentenyl]amino]propionate**

Prepared from (S)-ethyl-3-[4-[(2,6-naphthyridin-1-yl)amino]phenyl]-2-amino-propionate and Intermediate 8. δ H (DMSO-d₆) 9.30-9.20 (2H, m), 8.70 (1H, m), 8.40 (1H, br), 8.10 (1H, br m) 7.80 (2H, m), 7.20 (3H, m), 4.50
15 (1H, m), 4.10 (2H, m), 3.20-3.00 (2H, m), 2.30-2.00 (5H, m), 1.60 (2H, m), 1.40 (2H, m), 1.20 (3H, m), 0.80 (6H, t, \downarrow 7.5Hz). m/z (ESI, 70V) 487 (MH⁺).

EXAMPLE 37

20 **(S)-Ethyl-3-[(4-(3-methyl-2,7-naphthyridin-1-yl)oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediates 21 and 7. δ H (DMSO-d₆) 9.60 (1H, s), 8.73 (1H, d, \downarrow 5.7Hz), 7.76 (1H, d, \downarrow 5.8Hz), 7.39 (2H, d), 7.37 (1H, s), 7.22 (2H, d), 7.13 (1H, d), 4.47 (1H, m), 4.15 (2H, q, \downarrow 7.1Hz), 3.24 (1H, dd), 3.09
25 (1H, dd, \downarrow 13.7, 10.0Hz), 2.35 (1H, m), 2.35 (3H, s), 2.20-2.00 (3H, m), 1.91 (2H, d), 1.68 (1H, seq t), 1.20 (3H, t, \downarrow 7.1Hz), 0.78 (3H, d, \downarrow 6.6Hz), 0.78 (3H, d, \downarrow 6.6Hz). m/z (ESI, 70V) 488 (MH⁺).

EXAMPLE 38

30 **(S)-Ethyl-3-[(4-(2,7-naphthyridin-1-yl)oxy)phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediates 14 and 5. δ H (DMSO-d₆) 9.71 (1H, s), 8.83 (1H, d, \downarrow 5.7Hz), 8.13 (1H, d, \downarrow 5.8Hz), 7.91 (1H, d), 7.56 (1H, d, \downarrow 5.9Hz), 7.41 (2H, d, \downarrow 8.5Hz), 7.24 (3H, d), 4.46 (1H, m), 4.18 (2H, q, \downarrow 7.1Hz),
35 3.25 (1H, dd, \downarrow 13.6, 5.0Hz), 3.11 (1H, dd, \downarrow 13.5, 9.8Hz), 2.34 (1H, m),

2.17-2.00 (5H, m), 1.27 (2H, m), 1.23 (3H, t, \downarrow 7.1Hz), 0.82 (3H, t, \downarrow 7.3Hz). m/z (ESI, 70V) 460 (MH^+).

EXAMPLE 39**5 (S)-Ethyl-3-[(4-(2,7-naphthyridin-1-yl)oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediates 14 and 7. δH (DMSO- d_6) 9.74 (1H, s), 8.87 (1H, d, \downarrow 5.7Hz), 8.17 (1H, d, \downarrow 5.8Hz), 7.95 (2H, d, \downarrow 5.8Hz), 7.59 (1H, d, \downarrow 5.8Hz), 7.44 (2H, d, \downarrow 8.5Hz), 7.27 (2H, d, \downarrow 8.5Hz), 7.19 (1H, d, \downarrow 9.6Hz),
10 4.52 (1H, m), 4.21 (2H, q, \downarrow 7.1Hz), 3.30 (1H, dd, \downarrow 13.6, 5.0Hz), 3.15 (1H, dd, \downarrow 13.6, 9.9Hz), 2.56 (1H, m), 2.39-2.04 (3H, m), 1.97 (2H, d), 1.73 (1H, sept \downarrow 6.7Hz), 1.26 (2H, t, \downarrow 7.1Hz), 0.83 (3H, d, \downarrow 6.6Hz), 0.82 (3H, d, \downarrow 6.6Hz). m/z (ESI, 70V) 474 (MH^+).

15 EXAMPLE 40**(S)-Ethyl-3-[(4-(2,7-naphthyridin-1-yl)amino)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediates 13 and 7. δH (DMSO- d_6) 9.84 (1H, s), 8.67 (1H, d, \downarrow 5.6Hz), 8.17 (1H, d), 7.78 (2H, m), 7.70 (1H, d, \downarrow 5.6Hz), 7.27 (2H, d, \downarrow 8.5Hz), 7.14 (1H, d, \downarrow 5.7Hz), 7.09 (1H, d, \downarrow 9.4Hz), 4.42 (1H, m),
20 4.16 (2H, q, \downarrow 7.1Hz), 3.18 (1H, m), 4.16 (2H, q, \downarrow 7.1Hz), 3.18 (1H, dd, \downarrow 13.6, 4.9Hz), 3.05 (1H, dd, \downarrow 13.6, 9.7Hz), 2.36 (1H, m), 2.17-1.97 (5H, m), 1.69 (1H, m), 1.22 (3H, t, \downarrow 7.1Hz), 0.80 (6H, d, \downarrow 6.6Hz). m/z (ESI, 70V), 473 (MH^+).

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EXAMPLE 41**(S)-Ethyl-3-[(4-(3-methyl-2,7-naphthyridin-1-yl)amino)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from Intermediates 18 and 7 as an orange solid. δH (DMSO- d_6)
30 8.57 (1H, d), 7.87 (2H, d, \downarrow 8.3Hz), 7.57 (1H, d), 7.25 (2H, d, \downarrow 8.4Hz), 7.14 (1H, d), 6.97 (1H, s), 4.45 (1H, m), 4.17 (2H, q, \downarrow 7.4Hz), 3.17 (1H, dd, \downarrow 14.2, 4.9Hz), 3.05 (1H, dd, \downarrow 14.2, 10.2Hz), 2.44 (3H, s), 2.37 (1H, m), 2.16 (1H, m), 2.05 (2H, m), 1.92 (2H, d), 1.70 (1H, m), 1.21 (3H, t), 0.79 (6H, d); m/z (ESI, 70V) 487 (MH^+).

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EXAMPLE 42

(S)-Methyl-3-(4-[2',6'-dimethoxy]biphenyl)-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from the free amino of Intermediate 24 and Intermediate 7. δ H (DMSO- d_6) 7.26 (3H, m), 7.14 (2H, d, \downarrow 8.2Hz), 6.75 (2H, d, \downarrow 8.4Hz), 6.68 (1H, d, \downarrow 9.5Hz), 4.48 (1H, m), 3.73 (1H, s), 3.65 (1H, s), 3.25 (1H, dd, \downarrow 13.7, 5.0Hz), 3.10 (1H, dd, \downarrow 13.7, 9.3Hz), 2.35 (1H, m), 2.13-1.99 (3H, m), 1.95 (2H, d, \downarrow 7.2Hz), 1.77 (1H, seq, \downarrow 6.81Hz), 0.82 (3H, d, \downarrow 6.7Hz), 0.81 (3H, d, \downarrow 6.6Hz). m/z (ESI, 70V) 452 (MH^+).

10 **EXAMPLE 43**

Ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from Ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-aminopropionate and 2-ethyl-cyclopentane-1,3-dione. δ H (DMSO- d_6), 8.81 (2H, s), 7.64 (2H, d), 7.51 (1H, d), 7.45 (2H, d), 5.00 (1H, m), 4.10 (2H, q, \downarrow 7.1 Hz), 3.05 (1H, dd), 2.84 (1H, dd), 2.64 (1H, m), 2.31 (1H, m), 2.09 (4H, m), 1.17 (3H, t, \downarrow 7.09 Hz), 0.86 (3H, t, \downarrow 7.3 Hz). m/z (ESI, 70V) 491 (MH^+).

20 **EXAMPLE 44**

Ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-aminopropionate and Intermediate 5. δ H (DMSO- d_6), 8.89 (2H, s), 7.66 (2H, d), 7.47 (2H, d), 5.03 (1H, m), 4.11 (2H, q, \downarrow 7.3Hz), 3.08 (1H, dd), 2.88 (1H, dd), 2.73 (1H, m), 2.35 (1H, m), 2.09 (4H, m), 1.35 (2H, quin, \downarrow 7.13, 4.73Hz), 1.16 (3H, t, \downarrow 7.1Hz), 0.88 (3H, t, \downarrow 7.2Hz). m/z (ES+, 70V) 505 (MH^+).

30 **EXAMPLE 45**

Ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-aminopropionate (prepared according to the methods of International Patent Application WO 00/32575) and Intermediate 7. δ H (DMSO- d_6), 8.83 (2H, s), 7.65 (2H, d), 7.46 (2H, d), 7.40 (1H, d), 5.01 (1H, m), 4.12

(2H, q, \downarrow 7.14Hz), 2.98 (1H, m), 2.81 (2H, m), 2.33 (1H, m), 2.17 (2H, m), 1.99 (2H, m), 1.78 (1H, m), 1.17 (3H, t, \downarrow 7.1Hz), 0.85 (6H, d, \downarrow 6.55Hz). m/z (ES⁺, 70V) 519 (MH⁺).

5 **EXAMPLE 46**

Methyl-3-[4-({3,5-dichloropyrid-4-yl}carboxamido)phenyl]-3-[(2-butyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from methyl-3-[4-({3,5-dichloropyrid-4-yl}carboxamido)phenyl]-3-amino propionate (prepared according to the methods in International
10 Patent Application WO 00/18759) and Intermediate 3. δ H (DMSO- d_6) 8.80 (2H, s), 7.60 (2H, d), 7.42 (2H, d), 7.38 (1H, d), 4.98 (1H, m), 3.62 (3H, s), 3.05 (1H, dd), 2.87 (1H, dd), 2.38-1.95 (6H, m), 1.21 (4H, m), 0.42 (3H, t). m/z (ESI, 70V) 504 (MH⁺).

15 **EXAMPLE 47**

Methyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-phenyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from Methyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-aminopropionate and intermediate 4. δ H (CD₃OD) 8.66 (2H, s), 7.73-
20 7.17 (9H, 3 x m), 5.22 (1H, br), 3.77 (3H, s), 3.10-2.90 (2H, m), 2.57-2.45 (4H, m). m/z (ESI, 70V) 523 (MH⁺).

EXAMPLE 48

Ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-[(5-propyl-3-oxo-1-cyclohexenyl)amino]propionate

Prepared from ethyl-3-[4-(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-3-amino-propionate and 5-propyl-1,3-cyclohexanedione. δ H (DMSO- d_6),
25 8.80 (2H, s), 7.56 (2H, d), 7.46 (1H, d), 7.36 (2H, d), 4.71 (1H, m), 4.08 (2H, q, \downarrow 7.4Hz), 2.86 (1H, m), 2.74 (1H, m), 2.38 (1H, m), 2.09 (2H, m),
30 1.81 (2H, m), 1.32 (4H, m), 1.18 (3H, t), 0.88 (3H, t). m/z (ES⁺, 70V) 519 (MH⁺).

In a similar manner to Example 18 were prepared Examples 49 - 62.

35 **EXAMPLE 49**

(S)-3-[4-[(3-Methyl-2,7-naphthyridinyl)oxy]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid

Prepared from Example 35. δ H (DMSO- d_6) 9.34 (1H, s), 9.27 (1H, s), 8.72 (1H, d, \downarrow 5.8Hz), 8.45 (1H, d, \downarrow 5.9Hz), 8.18 (1H, d, \downarrow 5.7Hz), 7.80 (2H, d, \downarrow 8.4Hz), 7.32 (1H, d, \downarrow 5.7Hz), 7.24 (2H, d, \downarrow 8.4Hz), 6.67 (1H, d, \downarrow 8.8Hz), 4.15 (1H, br), 3.17 (1H, dd, \downarrow 13.5, 4.1Hz), 3.01 (1H, dd, \downarrow 13.2, 8.5Hz), 2.38 (1H, m), 2.21 (1H, m), 2.20-1.90 (3H, m), 1.75-1.60 (2H, m), 1.60-1.40 (2H, m), 0.78 (3H, t, \downarrow 7.1Hz), 0.77 (3H, t, \downarrow 7.4Hz); m/z (ESI, 70V) 459 (MH⁺).

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EXAMPLE 50

(S)-3-[4-[(2,6-Naphthyridinyl)amino]phenyl]-2-[(2-(1-ethylpropyl)-3-oxo-1-cyclopentenyl)amino]propionic acid

Prepared from Example 36. δ H (DMSO- d_6) 9.82 (1H, s), 8.75 (1H, d, \downarrow 5.7Hz), 7.98 (1H, d, \downarrow 5.8Hz), 7.43 (3H, d), 7.30 (1H, d), 4.56 (1H, m), 3.47 (1H, dd, \downarrow 13.6, 4.3Hz), 3.29 (1H, dd, \downarrow 13.6, 10.2Hz), 2.58 (3H, s), 2.55 (1H, m), 2.30-2.20 (5H, m), 1.47 (2H, m), 1.02 (3H, t, \downarrow 7.2Hz). m/z (ESI, 70V) 446 (MH⁺).

20 **EXAMPLE 51**

(S)-3-[4-[(3-Methyl-2,7-naphthyridinyl)oxy]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid

Prepared from Example 37. δ H (DMSO- d_6) 9.61 (1H, s), 8.74 (1H, d, \downarrow 5.7Hz), 7.77 (1H, d, \downarrow 5.7Hz), 7.39 (2H, d, \downarrow 8.3Hz), 7.37 (1H, s), 7.22 (2H, d, \downarrow 8.3Hz), 7.06 (1H, d, \downarrow 9.7Hz), 4.38 (1H, m), 3.26 (1H, dd ???), 3.09 (1H, dd, \downarrow 13.4, 10.3Hz), 2.33 (3H, s), 2.37 (1H, m), 2.10-1.85 (5H, m), 1.68 (1H, m), 0.78 (6H, m). m/z (ESI, 70V) 460 (MH⁺).

EXAMPLE 52

30 **(S)-3-[4-(2,7-naphthyridin-1-yl)oxy]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 38. δ H (DMSO- d_6) 9.71 (1H, s), 9.83 (1H, d, \downarrow 5.7Hz), 8.14 (1H, d, \downarrow 5.8Hz), 7.91 (1H, d, \downarrow 5.8Hz), 7.55 (1H, d, \downarrow 5.8Hz), 7.41 (2H, d, \downarrow 8.4Hz), 7.23 (2H, d, \downarrow 8.5Hz), 7.05 (1H, d), 4.36 (1H, m), 3.26 (1H, dd), 3.08 (1H, dd, \downarrow 13.5, 19.2Hz), 2.33 (1H, m), 2.01 (5H, m), 1.27 (2H, m), 0.82 (3H, t, \downarrow 7.3Hz). m/z (ESI, 70V) 432 (MH⁺).

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EXAMPLE 53**(S)-3-[(4-(2,7-Naphthyridin-1-yl)oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

- 5 Prepared from Example 39. δ H (DMSO- d_6) 9.70 (1H, s), 8.83 (1H, d, \downarrow 5.7Hz), 8.13 (1H, d, \downarrow 5.8Hz), 7.90 (1H, d, \downarrow 5.7Hz), 7.55 (1H, d, \downarrow 5.8Hz), 7.40 (2H, d, \downarrow 8.4Hz), 7.22 (2H, d, \downarrow 5.8Hz), 7.05 (1H, d), 4.38 (1H, m), 3.27 (1H, m) 3.08 (1H, dd, \downarrow 13.5, 10.1Hz), 2.36 (1H, m), 2.06 (3H, m), 1.91 (2H, d), 1.69 (1H, m), 0.79 (3H, d, \downarrow 6.6Hz), 0.78 (3H, d, \downarrow 6.6Hz). m/z
10 (ESI, 70V) 446 (MH⁺).

EXAMPLE 54**(S)-3-[4-[(2,7-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

- 15 Prepared from Example 40. δ H (DMSO- d_6) 9.83 (1H, s), 9.52 (1H, s), 8.66 (1H, d, \downarrow 5.6Hz), 8.16 (1H, d, \downarrow 5.7Hz), 7.73 (2H, d, \downarrow 8.4Hz), 7.69 (1H, d, \downarrow 5.6Hz), 7.22 (2H, d, \downarrow 8.4Hz), 7.13 (1H, d, \downarrow 5.6Hz), 4.13 (1H, br), 3.15 (1H, dd, \downarrow 13.6, 3.7Hz), 2.97 (1H, dd, \downarrow 13.2, 9.2Hz), 2.36 (1H, m), 2.10-1.88 (5H, m), 1.69 (1H, m), 0.80 (3H, d, \downarrow 6.3Hz), 0.79 (3H, d, \downarrow 6.4Hz). m/z (ESI, 70V) 445 (MH⁺).

EXAMPLE 55**(S)-3-[4-[(3-Methyl-2,7-naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

- 25 Prepared from Example 41. δ H (DMSO- d_6) 8.55 (1H, d), 7.86 (2H, d, \downarrow 8.2Hz), 7.56 (1H, d), 7.24 (2H, d, \downarrow 8.3Hz), 7.15 (1H, d), 6.96 (1H, s), 4.43 (1H, m), 3.17 (1H, dd, \downarrow 14.1, 5.8Hz), 3.04 (1H, dd, \downarrow 14.1, 10.1Hz), 2.43 (3H, s), 2.36 (1H, m), 2.15 (1H, m), 1.91 (2H, d), 1.71 (1H, m), 1.22 (3H, t), 0.78 (6H, d). m/z (ESI, 70V) 459 (MH⁺).

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EXAMPLE 56**(S)-3-[4-(-2',6'-Dimethoxy)biphenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

- Prepared from Example 42. δ H (DMSO- d_6) 7.27 (3H, m), 7.09 (3H, d),
35 6.72 (2H, d, \downarrow 8.4Hz), 4.36 (1H, m), 3.64 (6H, s), 3.24 (1H, dd, \downarrow 13.6, 4.2Hz), 3.03 (1H, dd, \downarrow 13.6, 10.2Hz), 2.32 (1H, m), 2.06 (1H, m), 1.97-

1.91 (4H, m), 1.72 (1H, m), 0.79 (6H, d, \downarrow 6.5Hz). m/z (ESI, 70V) 438 (MH⁺).

EXAMPLE 57

5 **3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 43. δ H NMR (DMSO-d⁶), 8.79 (2H, s), 7.62 (2H, d), 7.49 (1H, d), 7.42 (2H, d), 4.97 (1H, m), 3.03 (1H, dd), 2.82 (1H, dd), 2.62 (1H, m), 2.29 (1H, m), 2.07 (4H, m), 0.85 (3H, t, \downarrow 7.3Hz). m/z (ES+, 70V) 463 (MH⁺).

EXAMPLE 58

15 **3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 44. δ H NMR (DMSO-d⁶), 8.85 (2H, s), 7.63 (2H, d), 7.45 (2H, d), 4.98 (1H, m), 3.04 (1H, dd), 2.85 (1H, dd), 2.71 (1H, m), 2.31 (1H, m), 2.05 (4H, m), 1.33 (2H, quin, \downarrow 7.13, 4.73Hz), 0.89 (3H, t, \downarrow 7.2Hz). m/z (ES+, 70V) 477 (MH⁺).

EXAMPLE 59

20 **3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 45. δ H NMR (DMSO-d⁶), 8.81 (2H, s), 7.63 (2H, d), 7.44 (2H, d), 7.38 (1H, d), 4.97 (1H, m), 2.96 (1H, m), 2.79 (2H, m), 2.31 (1H, m), 2.15 (2H, m), 1.96 (2H, m), 1.75 (1H, m), 0.82 (6H, d, \downarrow 6.54Hz). m/z (ES+, 70V) 491 (MH⁺).

EXAMPLE 60

30 **3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-butyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 46. δ H (DMSO-d⁶) 10.89 (1H, s), 8.76 (2H, s), 7.58 (2H, d, \downarrow 8.5Hz), 7.38 (3H, d), 4.90 (1H, m), 2.88 (1H, m), 2.71 (1H, dd, \downarrow 15.9, 4.9Hz), 2.63 (1H, m), 2.21 (1H, m), 2.10-2.00 (4H, m), 1.20 (4H, br), 0.82 (3H, t, \downarrow 6.9Hz). m/z (ESI, 70V) 489 (MH⁺).

EXAMPLE 61

3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-3-[(2-phenyl-3-oxo-1-cyclopentenyl)amino]propionic acid

- Prepared from Example 47. δ H (DMSO- d_6) 11.00 (1H, s), 8.85 (1H, s), 7.98 (1H, br), 7.70 (2H, d, \downarrow 8.0Hz), 7.52 (2H, d, \downarrow 8.0Hz), 7.41 (4H, m), 7.27 (1H, m), 5.12 (1H, br), 3.08 (1H, m), 2.88 (1H, m), 2.73 (1H, m), 2.49 (1H, m), 2.32 (2H, m). m/z (ESI, 70V) 510 (MH^+).

EXAMPLE 62

- 3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-3-[(5-propyl-3-oxo-1-cyclohexenyl)amino]propionic acid**

- Prepared from Example 48. δ H NMR (DMSO- d_6) 8.80 (2H, s), 7.60 (2H, d), 7.53 (1H, d), 7.35 (2H, d), 4.71 (1H, m), 2.81 (1H, m), 2.68 (1H, m), 2.40 (1H, m), 2.10 (2H, m), 1.81 (2H, m), 1.29 (4H, m), 0.88 (3H, t). m/z (ES+, 70V) 491 (MH^+).

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In a similar manner to Example 35 were prepared Examples 63-66:

EXAMPLE 63

- Ethyl-3-[5-[(3-methyl-2,7-naphthyridin-1-yl)oxy]pyridin-2-yl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionate**

- Prepared from intermediates 29 and 5. δ H ($CDCl_3$) 9.72 (1H, s), 8.73 (1H, d, \downarrow 5.8Hz), 8.59 (1H, d, \downarrow 2.6Hz), 7.65 (1H, dd, \downarrow 8.4, 2.7Hz), 7.54 (1H, d, \downarrow 5.8Hz), 7.26 (1H, d, \downarrow 8.4Hz), 7.17 (1H, s), 6.51 (1H, d, \downarrow 9.3Hz), 4.67-4.61 (1H, symm. m), 4.20 (2H, q, \downarrow 7.1Hz), 3.45-3.37 (2H, m), 2.45 (3H, s), 2.52-2.31 (4H, m), 2.14 (2H, qd, \downarrow 14.6, 7.5Hz), 1.46 (2H, hextet, \downarrow 7.4Hz), 1.23 (3H, t, \downarrow 7.1Hz) and 0.92 (3H, t, \downarrow 7.3Hz); m/z (ES+, 70V) 475 (MH^+).

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EXAMPLE 64

- Ethyl-3-[5-[(3-methyl-2,7-naphthyridin-1-yl)oxy]pyridin-2-yl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate**

- Prepared from Intermediates 29 and 7. δ H ($CDCl_3$) 9.63 (1H, s), 8.64 (1H, d, \downarrow 5.8Hz), 8.51 (1H, d, \downarrow 2.7Hz), 7.56 (1H, dd, \downarrow 8.4, 2.7Hz), 7.45 (1H, dd, \downarrow 5.8, 0.7Hz), 7.17 (1H, d, \downarrow 8.4Hz), 7.08 (1H, s), 6.49 (1H, d, \downarrow 9.2Hz), 4.59-4.52 (1H, m), 4.11 (2H, q, \downarrow 7.1Hz), 3.34-3.32 (2H, m), 2.45-2.27 (4H, m), 2.37 (3H, s), 1.95 (2H, qd, \downarrow 13.9, 7.2Hz), 1.75 (1H, m), 1.14 (3H, t, \downarrow

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7.1Hz), 0.82 (3H, d, \downarrow 6.2Hz) and 0.80 (3H, d, \downarrow 6.2Hz), m/z (ES⁺, 70V) 489 (MH⁺).

EXAMPLE 65

5 Ethyl-3-[5-[(3-methyl-2,7-naphthyridin-1-yl)oxy]-pyridin-2-yl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from Intermediate 29 and 2-ethyl-1,3-cyclopentanedione. δ H (CDCl₃) 9.63 (1H, s), 8.64 (1H, d, \downarrow 5.8Hz), 8.51 (1H, d, \downarrow 2.6Hz), 7.56 (1H, dd, \downarrow 8.4, 2.7Hz), 7.46 (1H, dd, \downarrow 5.8, 0.8Hz), 7.18 (1H, d, \downarrow 8.4Hz),
 10 7.08 (1H, s), 6.34 (1H, d, \downarrow 9.3Hz), 4.59-4.52 (1H, m), 4.12 (2H, q, \downarrow 7.1Hz), 3.39-3.29 (2H, m), 2.37 (3H, s), 2.38-2.25 (4H, m), 2.17-2.03 (2H, m), 1.16 (3H, t, \downarrow 7.1Hz) and 0.93 (3H, t, \downarrow 7.5Hz); m/z (ES⁺, 70V) 461 (MH⁺).

15 EXAMPLE 66

(S)-Ethyl-3-[4-[(3,5-dichloropyrid-4-yl)carboxamide]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate

Prepared from (S)-ethyl-3-[4-[(3,5-dichloropyrid-4-yl)carboxamido]phenyl]-2-aminopropionate and Intermediate 7. δ H (MeOD) 8.55 (2H, s), 7.50 (2H, d, \downarrow 8.5Hz), 7.19 (2H, d, \downarrow 8.5Hz), 4.41 (1H, dd, \downarrow 9.8, 4.7Hz); 4.16 (1H, q, \downarrow 7.2Hz), 4.13 (1H, q, \downarrow 7.2Hz), 3.23 (1H, dd, \downarrow 13.9, 4.6Hz), 2.97 (1H, dd, \downarrow 13.9, 9.9Hz), 2.38 (1H, m), 2.18 (3H, m), 1.88 (2H, d, \downarrow 7.3Hz), 1.58 (1H, septet, \downarrow 6.9Hz), 1.19 (3H, \downarrow 7.2Hz), 0.72 (6H, dd, \downarrow 6.9, 1.5Hz); m/z (ES⁺, 70V) 518 (MH⁺).

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To a similar manner to Example 18 were prepared Examples 67 - 70.

EXAMPLE 67

30 3-[5-[(3-Methyl-2,7-naphthyridin-1-yl)oxy]-pyridin-2-yl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid

Prepared from Example 63. δ H (DMSO-d₆) 9.65 (1H, s), 8.76 (1H, d, \downarrow 5.8Hz), 8.55 (1H, d, \downarrow 2.7Hz), 7.79 (1H, d, \downarrow 5.8Hz), 7.77 (1H, dd, \downarrow 8.4, 2.7Hz), 7.43 (1H, d, \downarrow 8.4Hz), 7.41 (1H, s), 7.22 (1H, d, \downarrow 9.6Hz), 4.65 (1H, narrow, m), 3.40 (1H, dd, \downarrow 14.1, 4.5Hz), 3.31 (1H, dd, \downarrow 14.1, 9.9Hz), 2.43-
 35 2.37 (1H, m), 2.38 (3H, s), 2.27-2.22 (1H, m), 2.09-2.05 (2H, m), 2.04-1.97

(2H, m), 1.24 (2H, hextet, \downarrow 7.4Hz), and 0.79 (3H, t, \downarrow 7.3Hz); m/z (ES^+ , 70V) 447 (MH^+).

EXAMPLE 68

5 **3-[5-[(3-Methyl-2,7-naphthyridin-1-yl)oxyl]-pyridin-2-yl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 64. δH (DMSO- d_6) 9.65 (1H, s), 8.76 (1H, d, \downarrow 5.7Hz), 8.57 (1H, d, \downarrow 2.7Hz), 7.79 (1H, d, \downarrow 5.8Hz), 7.74 (1H, dd, \downarrow 8.4, 2.7Hz), 7.41 (1H, s), 7.41 (1H, d, \downarrow 8.4Hz), 7.11 (1H, d, \downarrow 9.3Hz), 4.60 (1H, m), 3.40 (1H, m), 3.30 (1H, m), 2.45-2.40 (1H, m), 2.37 (3H, s), 2.27-2.22 (1H, m), 2.15-2.00 (2H, m), 1.95-1.82 (2H, m), 1.65 (1H, m), 0.77 (3H, d, \downarrow 6.6Hz), and 0.72 (3H, d, \downarrow 6.6Hz); m/z (ES^+ , 70V) 461 (MH^+).

EXAMPLE 69

15 **3-[5-[(3-Methyl-2,7-naphthyridin-1-yl)oxyl]-pyridin-2-yl]-2-[(2-ethyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 65. δH (DMSO- d_6) 9.65 (1H, s), 8.76 (1H, d, \downarrow 5.7Hz), 8.58 (1H, d, \downarrow 2.7Hz), 7.80-7.76 (2H, overlapping signals), 7.44 (1H, d, \downarrow 8.5Hz), 7.41 (1H, s), 7.24 (1H, d, \downarrow 9.5Hz), 4.65 (1H, m), 3.40 (1H, dd, \downarrow 14.1, 4.5Hz), 3.31 (1H, dd, \downarrow 14.1, 9.5Hz), 2.43-2.39 (1H, m), 2.38 (3H, s), 2.26-2.20 (1H, m), 2.08-2.00 (4H, m) and 0.82 (3H, t, \downarrow 7.4Hz); m/z (ES^+ , 70V) 433 (MH^+).

EXAMPLE 70

25 **(S)-3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 66. δH (MeOD) 8.67 (2H, s), 7.59 (2H, d, \downarrow 8.5Hz), 7.31 (2H, d, \downarrow 8.5Hz), 4.46 (1H, dd, \downarrow 9.8, 4.2Hz), 3.37 (1H, dd, \downarrow 13.9, 10.0Hz), 2.50 (1H, dd, \downarrow 14.2, 4.9Hz), 2.22 (3H, m), 1.99 (2H, d, \downarrow 5.2Hz), 1.69 (1H, septet, \downarrow 6.6Hz), 0.82 (6H, d, \downarrow 6.6Hz). m/z (ES^+ , 70V) 491 (MH^+).

EXAMPLE 71

35 **(S)-Ethyl-3-[4-[(3-methyl-2,7-naphthyridin-1-yl)amino]phenyl]-2-[(2-cyclohexyl-3-oxo-1-cyclopentenyl)amino]propionate**

Prepared from the Intermediate 9 and the Intermediate 19 in a similar manner to Example 35. δ H (DMSO- d_6) 9.77 (1H, s), 9.47 (1H, s), 8.59 (1H, d, \downarrow 6.0Hz), 7.88 (2H, d, \downarrow 4.0Hz), 7.85 (1H, d, \downarrow 5.0Hz), 7.84 (2H, d, \downarrow 3.0Hz), 7.57 (1H, s), 7.24 (1H, d, \downarrow 8.0Hz), 4.40 (1H, m), 4.18 (2H, q, \downarrow 7.0Hz), 3.19 (1H, dd, \downarrow 14.0, 5.0Hz), 3.08 (1H, dd, \downarrow 14.0, 9.0Hz), 2.44 (3H, s), 2.35 (1H, m), 2.33 (1H, m), 2.29 (1H, m), 1.83 (3H, s), 1.80 (2H, m), 1.70 (5H, m), 1.63 (5H, m), 1.30 (3H, m). m/z (ES⁺, 70V) 512 (MH⁺).

EXAMPLE 72

10 **(S)-3-[4-((3-Methyl-2,7-naphthyridin-1-yl)amino)phenyl]-2-[(2-cyclohexyl-3-oxo-1-cyclopentenyl)amino]propionic acid**

Prepared from Example 71 in a similar manner to Example 18. δ H (DMSO- d_6) 9.75 (1H, s), 8.58 (1H, d, \downarrow 6.0Hz), 7.87 (2H, d, \downarrow 8.0Hz), 7.54 (1H, d, \downarrow 6.0Hz), 7.25 (2H, d, \downarrow 8.0Hz), 6.96 (1H, s), 6.31 (1H, br s), (4.27 15 (1H, m), 3.21 (1H, dd, \downarrow 14.0, 4.0Hz), 3.09 (1H, dd, \downarrow 14.0, 8.0Hz), 2.47 (3H, s), 2.39 (2H, m), 2.35 (3H, s), 2.08 (2H, m), 1.75 (5H, m), 1.39 (5H, m). m/z (ES⁺, 70V) 485 (MH⁺).

EXAMPLE 73

20 **(S)-Ethyl-3-[4-((3,5-dichloropyrid-4-yl)carboxamido)phenyl]-2-[(4,5-dihydro-1,1-dioxothiophen-3-yl)amino]propionate**

(S)-Ethyl-3-[4-((3,5-dichloropyrid-4-yl)carboxamido)phenyl]-2-amino-propionate (500mg, 1.3mmol) was added to Intermediate 30 (340mg, 2.54mmol) in 1,2-DCE (5ml) and 3 drops of glacial acetic acid added. The mixture was heated at 90° for 16h, cooled, concentrated and purified by column chromatography (SiO₂; CH₂Cl₂/MeOH 100:1) to give the title compound (320mg, 0.64mmol, 49%) as an off white solid. δ H (DMSO- d_6) 10.89 (1H, s), 8.81 (2H, s), 7.59 (2H, d, \downarrow 8.5Hz), 7.26 (2H, d, \downarrow 8.5Hz), 7.20 (1H, d, \downarrow 8.2Hz), 5.31 (1H, s z), 4.04 (1H, m), 3.22 (2H, t, \downarrow 6.9Hz), 30 3.05 (1H, dd, \downarrow 13.8, 6.0Hz), 2.96 (1H, dd, \downarrow 13.8, 7.9 Hz), 2.82 (1H, dd, \downarrow 16.6, 6.5Hz), 2.73 (1H, dd, \downarrow 16.6, 6.8Hz), 1.18 (3H, t, \downarrow 7.1Hz). m/z (ES⁺, 70V), 498 (MH⁺).

EXAMPLE 74

35 **(S)-3-[4-((3,5-Dichloropyrid-4-yl)carboxamido)phenyl]-2-[(4,5-dihydro-1,1-dioxothiophen-3-yl)amino]propionic acid**

Prepared from Example 73 in a similar manner to Example 18. δ H (DMSO- d_6) 10.90 (1H, s), 8.81 (2H, s), 7.56 (2H, d, \downarrow 8.2Hz), 7.23 (2H, d, \downarrow 8.2Hz), 5.25 (1H, s), 3.89 (1H, m), 3.20 (2H, t, \downarrow 6.9Hz), 3.05 (1H, dd, \downarrow 13.8, 5.7Hz), 2.92 (1H, dd, \downarrow 13.8, 7.3Hz), 2.76 (2H, m). m/z (ES^+ , 70V) 470 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with F(ab) $_2$ fragment goat anti-human IgG Fc γ -specific antibody [Jackson Immuno Research 109-006-098: 100 μ l at 2 μ g/ml in 0.1M NaHCO $_3$, pH 8.4], overnight at 4 $^\circ$. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37 $^\circ$ for 30 min in a total volume of 200 μ l containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100 μ l methanol for 10 minutes followed by another wash. 100 μ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 μ l 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_1$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-

line of the β -lympho blastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

5 **$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin**

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 μ l PBS/1% BSA at room temperature on a rocking platform. The
10 blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5x 10⁵ K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

15

$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10⁵ freshly isolated human venous polymorphonuclear
20 neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma
25 H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium
30 acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

$\alpha_{IIb}\beta_3$ -dependent human platelet aggregation

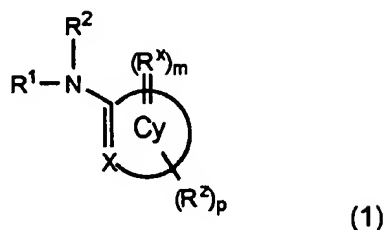
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich
35 plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and

5 diluted to a cell density of 6×10^8 /ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $\text{MgCl}_2 \cdot \text{H}_2\text{O}$ 0.427; CaCl_2 0.2; KCl 0.2; D-glucose 1.0; NaHCO_3 1.0; $\text{NaHPO}_4 \cdot 2\text{H}_2\text{O}$ 0.065). Aggregation was monitored following addition of 2.5 μM ADP (Sigma) in the presence or absence of inhibitors.

10 In the above assays the preferred compounds of the invention in which R^1 is an α_4 integrin binding group, such as the compounds of the Examples generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50 μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

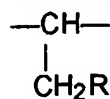
CLAIMS

1. A compound according to formula (1):



wherein

R¹ is a group Ar¹L²Ar²Alk- in which Ar¹ is an optionally substituted aromatic or heteroaromatic group, L² is a covalent bond or a linker atom or group, Ar² is an optionally substituted arylene or heteroarylene group and Alk is a chain -CH₂-CH(R)-, -CH=C(R)-,



in which R is a carboxylic acid (-CO₂H) or a derivative or biostere thereof;

R² is a hydrogen atom or a C₁₋₆alkyl group;

the ring Cy is an unsaturated cycloaliphatic or heterocycloaliphatic ring containing X, in which X is a N atom or a C(R^w) group;

R^w is a group R^z;

R^x which may be present on any available carbon atom of the ring Cy is a oxo (=O), thioxo (=S) or imino (=NR³⁰) group in which R³⁰ is an aliphatic, heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or hetero-aromatic group;

m is zero or the integer 1, 2 or 3;

R^z which may be present on any available carbon or nitrogen atom of the ring Cy is selected from a halogen atom or -(Alk⁴)_vL¹(Alk¹)_nR³ in which Alk⁴ is a straight or branched C₁₋₃alkylene chain, v is zero or the integer 1, L¹ is a covalent bond or a linker atom or group, n is zero or the integer 1, Alk¹ is an optionally substituted aliphatic chain and R³ is a hydrogen atom or a -CN, -NO₂ or an optionally

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- substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or hetero-aromatic group;
 p is zero or the integer 1, 2, 3 or 4;
 5 provided that Cy is not a cyclobutenedione group;
 and the salts, solvates, hydrates and N-oxides thereof.
2. A compound according to Claim 1 in which Alk is a chain:
 10
$$\begin{array}{c} \text{-CH-CH(R)-} \text{ or } \text{-CH-} \\ | \\ \text{CH}_2\text{R} \end{array}$$
3. A compound according to Claim 1 or Claim 2 in which R is a carboxylic acid (-CO₂H) group.
 15
4. A compound according to Claim 1 or Claim 2 in which R is an esterified carboxyl group of formula -CO₂Alk⁷.
5. A compound according to any one of Claims 1 to 4 in which R² is a
 20 hydrogen atom.
6. A compound according to any one of Claims 1 to 5 in which Ar² is an optionally substituted phenylene group.
- 25 7. A compound according to any one of Claims 1 to 6 in which Ar¹ is an optionally substituted phenyl or five-, six- or ten-membered heteroaromatic group.
8. A compound according to Claim 7 in which Ar¹ is an optionally
 30 substituted pyridyl, pyrimidinyl, naphthyridinyl, quinolinyl or isoquinolinyl group.
9. A compound according to any one of Claims 1 to 8 in which Cy is an optionally substituted unsaturated cycloaliphatic or heterocyclo-
 35 aliphatic ring in which m is the integer 1 and R^x is an oxo (=O) substituent.

10. A compound according to Claim 9 in which Cy is an optionally substituted cyclopentenyl, cyclohexenyl, cycloheptenyl, dihydro-pyrimidinyl, dihydropyridinyl or imidazoliny group.
- 5 11. A compound according to any one of Claims 1 to 9 in which X is a N atom.
- 10 12. A compound according to Claim 11 in which Cy is an optionally substituted 2-aminopyridin-4-one [where amino refers to the group -N(R²)-], 4-aminopyrimidin-2-one, 2-aminopyridin-4-one, 6-amino-pyridin-2-one or 2-aminoimidazolin-4-one ring.
- 15 13. A compound according to any one of Claim 1 to 9 in which X is a C(R^w) group.
- 20 14. A compound according to Claim 13 in which Cy is an optionally substituted 3-amino-2-cyclopenten-1-one [where amino refers to the group -N(R²)-] or 3-amino-2-cyclohexen-1-one ring.
- 25 15. A compound according to Claim 14 in which p is zero or the integer 1 or 2.
- 30 16. A compound according to any one of Claims 1 to 15 in which v in the group R^z is zero, Alk¹ is an aliphatic chain and R³ is a hydrogen atom.
17. A compound according to Claim 16 in which -Alk¹R³ is an optionally substituted C₁₋₆alkyl, allyl, (-CH₂CH=CH₂) or propargyl (-CH₂CCH) group.
18. A compound according to Claim 17 in which L¹ is a covalent bond.
- 35 19. A compound which is:
(S)-3-[4-[(2,6-Naphthyridinyl)amino]phenyl]-2-[(2-(1-ethylpropyl)-3-oxo-1-cyclopentenyl)amino]propionic acid;

- (S)-3-[4-[(3-Methyl-2,7-naphthyridinyl)oxy]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- (S)-3-[(4-[3-Methyl-2,7-naphthyridinyl]oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- 5 (S)-3-[(4-(2,7-Naphthyridin-1-yl)oxy)phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- (S)-3-[4-[(3,5-Dichloropyrid-4-yl)carboxamido]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- (S)-3-[4-[(3-Methyl-2,7-naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- 10 (S)-3-[4-(-2',6'-Dimethoxy)biphenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isobutyl-3-oxo-1-cyclopentenyl)amino]propionate;
- 15 (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-isopropyl-3-oxo-1-cyclopentenyl)amino]propionic acid;
- (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-allyl-3-oxo-1-cyclopentenyl)amino]propionate;
- (2S)-3-[4-(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-propyl-3-oxo-1-cyclopentenyl)amino]propionate;
- 20 and the salts, solvates, hydrates and N-oxides and carboxylic acid ester, particularly methyl, ethyl, propyl and i-propyl esters thereof.
20. A pharmaceutical composition comprising a compound according to
- 25 Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.